Highly Flexible Synthesis of 2-Arylethylamine Derivatives

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Keywords: Alkynes / Aminations / Homogeneous catalysis / Palladium / Titanium

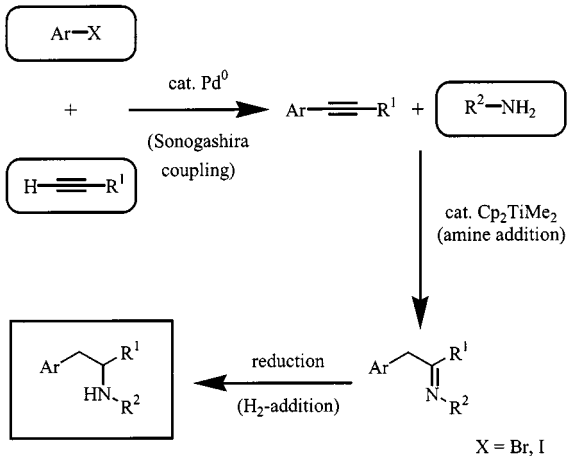
A new and highly flexible procedure for the synthesis of 2-arylethylamine derivatives is described. By the new procedure, the target compounds can be synthesized with high diversity in three steps from aryl halides, terminal alkynes, and primary amines. The reaction sequence starts with a palladium-catalyzed coupling of an aryl halide and a terminal alkyne (Sonogashira coupling). A subsequent Cp_2TiMe_2-catalyzed hydroamination of the obtained alkyl(aryl)alkyne, which takes place regioselectively in the 2-position, gives access to an α-arylketimine. A final reduction with $NaBH_3CN$/$ZnCl_2$·Et_2O results in the formation of the desired 2-arylethylamine derivative.

Introduction

Thanks to their high biological activity, 2-arylethylamine derivatives are of considerable interest for medicinal chemistry.[1] From a chemical point of view, they also represent interesting building blocks for the synthesis of complex nitrogen-containing molecules. Among the class of 2-arylethylamines, 2-phenylethylamine derivatives have attracted most attention. Because of their well-established effects on the central and vegetative nervous system, several 2-phenylethylamines are commonly used as drugs to treat diseases such as depression, asthma, or allergies. Well-known 2-phenylethylamine derivatives are adrenaline, noradrenaline, dopamine, mescaline, and amphetamine. Extensive investigations have shown that the greatly differing biological effects of such derivatives are caused by relatively small differences in their molecular structures. In contrast to that of 2-phenylethylamine derivatives, knowledge about the biological activity of 2-arylethylamines, in which aryl stands for thiophene, furan, pyrrole, pyridine, thiazole, etc., is limited.[2] One reason for this is that general methods for the synthesis of 2-arylethylamine derivatives, giving access to a wide variety of compounds, are rare.[3] In view of this, we set out to develop a highly flexible procedure for the synthesis of 2-arylethylamine derivatives, that would offer the potential to synthesize a large number of different products in a short time. Such a synthetic method, in combination with a high throughput screening for biological activity, would offer the potential to obtain detailed information about the relationships between structure and activity in 2-arylethylamine derivatives. In this publication we describe a new and highly flexible procedure for the synthesis of a wide variety of 2-arylethylamine derivatives.

Results and Discussion

The procedure for the synthesis of 2-arylethylamine derivatives is characterized by the fact that the target compounds can be synthesized with high diversity in three steps, starting from three sets of commercially available building blocks: aryl halides, terminal alkynes, and primary amines. The reaction sequence (Scheme 1) starts with a palladium-catalyzed coupling between an aryl halide and a terminal alkyne (Sonogashira coupling).[4] A subsequent Cp_2TiMe_2[5]-catalyzed hydroamination of the obtained alkyl(aryl)alkyne (amine addition), which takes place regioselectively in the 2-position, gives access to an α-arylketimine.[6] A final reduction of the formed imine (H_2 addi-



Scheme 1. Highly flexible synthesis of 2-arylethylamine derivatives from aryl halides, terminal alkynes, and primary amines

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tion) results in the formation of the desired 2-arylethylamine derivative.

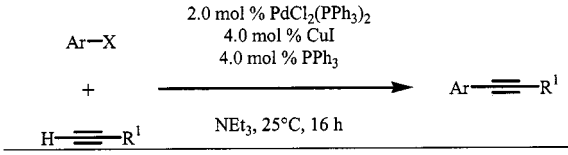
From a mathematical point of view, 20 aryl halides, 20 terminal alkynes, and 20 primary amines can be converted into 8000 different 2-arylethylamine derivatives by the described synthetic approach. A further advantage of the new process is the fact that, in principle, two addition reactions can be used and hydrogen iodide or bromide formed in the Sonogashira coupling is the only unavoidable side product.

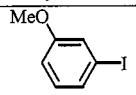
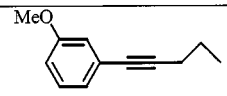
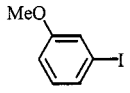
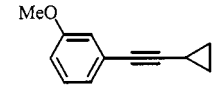
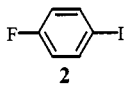
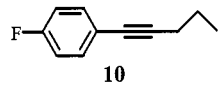
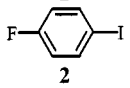
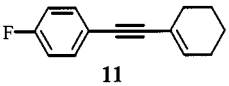
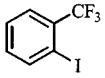
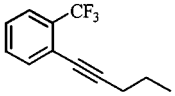
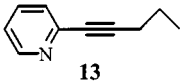
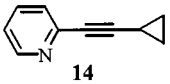
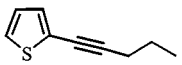
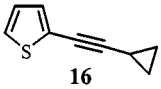
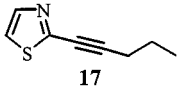
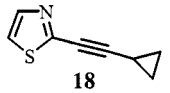
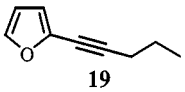
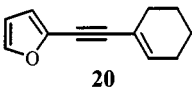
To demonstrate the efficiency of the developed process, we first coupled the commercially available aryl halides **1**−**6** and the easily accessible 2-iodofuran (**7**)[7] with three representative terminal alkynes (1-pentyne, cyclopropylacetylene as a 70% solution in toluene, and 1-ethynylcyclohexene) in various combinations (Table 1). The coupling reactions were usually performed under standard Sonogashira conditions in the presence of $PdCl_2(PPh_3)_2$ and CuI. Since coupling reactions employing 2-bromo-1,3-thiazole (**6**) did not give satisfactory yields (< 20%) under these conditions, it was necessary to use a catalyst system consisting of $PdCl_2(PhCN)_2$, PPh_3, and $Cu(OAc)_2{\cdot}H_2O$ for this substrate.[8] As can be seen from Table 1, all coupling reactions gave access to the desired alkyl(aryl)alkynes **8**−**20** in modest to excellent yields. In reactions with modest yields it was possible to isolate the corresponding diacetylenes formed by Glaser coupling. Optimization has not yet been carried out, however.

The obtained alkyl(aryl)alkynes **8**−**20** were then hydroaminated with the representative primary amines *tert*-butylamine, 4-methoxyaniline, 4-methylaniline, benzhydrylamine, and benzylamine. The reactions were carried out at 110 °C in the absence of solvent. Usually, 5.0 mol % Cp_2TiMe_2 were used and the ratio between alkyne and amine was 1:1. As observed previously,[6] the performed amine additions took place regioselectively in the 2-position of the employed alkyl(aryl)alkyne (*anti*-Markovnikov addition). With one exception, formation of the regioisomeric Markovnikov products could be observed only in trace amounts (< 2% by ^{1}H NMR spectroscopy). When, however, alkyne **11** was treated with *tert*-butylamine, the *anti*-Markovnikov selectivity was only 3:1. With three exceptions, all hydroamination reactions reached complete conversion within 12−15 h. The only reactions not to go to completion were those employing the 2-trifluoromethyl-substituted phenylalkyne **12** or benzylamine[6a][6b][6d] and the reaction between **11** and *tert*-butylamine. In control experiments performed under identical reaction conditions in the absence of Cp_2TiMe_2, no amine addition was observed at all. Even the Michael acceptors **13** and **14** did not undergo any reaction during 72 h.

The imines obtained from the hydroamination step, which were highly sensitive to hydrolysis, were not isolated but were directly reduced to the desired secondary amines. Several attempts to reduce the imines in situ with hydride donors such as $NaBH_3CN$, $LiAlH_4$, DIBAL-H, $NaBHEt_3$, and $NaBH(OAc)_3$, as well as catalytic hydrogenation in the presence of Pd/C and Pt/C (H_2 pressure up to 80 atm), gave access to the target compounds only in low yields

Table 1. Synthesis of alkyl(aryl)alkynes by Sonogashira coupling



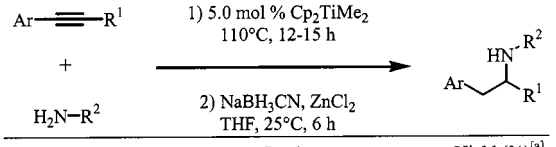
Entry	Aryl halide	Product	Yield (%)[a]
1	 **1**	 **8**	85
2	 **1**	 **9**	54
3	 **2**	 **10**	61
4	 **2**	 **11**	67
5	 **3**	 **12**	53
6	 **4**	 **13**	100
7	 **4**	 **14**	99
8	 **5**	 **15**	84
9	 **5**	 **16**	100
10	 **6**	 **17**	54[b]
11	 **6**	 **18**	63[b]
12	 **7**	 **19**	45
13	 **7**	 **20**	81

[a] Reaction conditions: aryl halide (10 mmol), alkyne (10 mmol), $PdCl_2(PPh_3)_2$ (0.2 mmol, 2.0 mol %), CuI (0.4 mmol, 4.0 mol %), PPh_3 (0.4 mmol, 4.0 mol %), NEt_3, 25 °C, 16 h; yields represent isolated yields of pure compounds. [b] Different reaction conditions were used for coupling reactions involving 2-bromo-1,3-thiazole (**6**): aryl halide (10 mmol), alkyne (10 mmol), $PdCl_2(PhCN)_2$ (0.5 mmol, 5.0 mol %), PPh_3 (1.0 mmol, 10.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol, 5.0 mol %), diisopropylamine, 45 °C, 12 h.

(10−40%). Finally, we found that an in situ reduction with 2 equiv. of $NaBH_3CN$ in the presence of 1 equiv. of $ZnCl_2{\cdot}Et_2O$ performed in THF at 25 °C gave the best results. Under these conditions the 2-arylethylamine derivatives **21**−**35** could be obtained in good yields, as summarized in Table 2.

Since titanium is a highly oxophilic metal it is remarkable that the hydroamination catalyst Cp_2TiMe_2 tolerates both ether (Entries 1, 2, 5, 6, 12) and aromatic (Entries 14, 15) oxygen atoms in the substrates. Therefore, furan derivatives (**34**, **35**) can be synthesized as well as phenyl (**21**−**25**), pyridine (**26**−**28**), thiophene (**29**, **30**) and thiazole (**31**−**33**) derivatives. Carbon−carbon double bonds (**11**, **20**) and cyclopropyl groups (**9**, **14**, **16**, **18**) are also tolerated under the reaction conditions and do not result in side reactions. Furthermore, the possible reductive removal of the benzhydryl groups in **27**, **30**, and **33** should allow the synthesis of primary amine derivatives.[6b] Oxidative cleavage of the 4-methoxyphenyl groups in **21**, **25**, **26**, and **32** should be possible as well.[9]

Table 2. Synthesis of 2-arylethylamine derivatives by regioselective hydroamination of alkyl(aryl)alkynes and subsequent in situ reduction



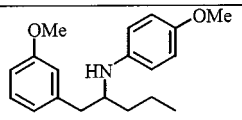
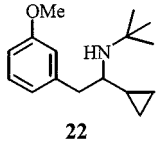
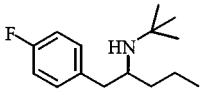
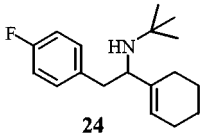
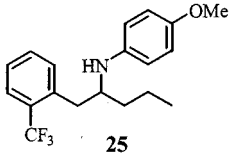
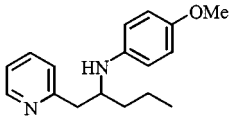
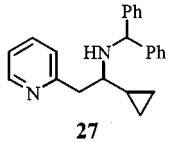
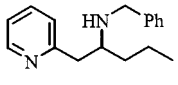
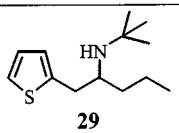
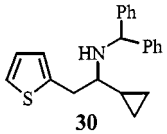
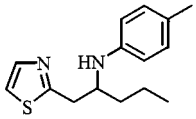
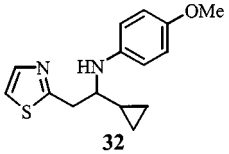
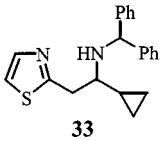
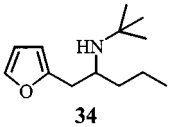
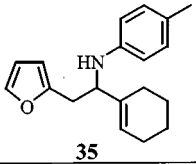
Entry	Alkyne	Product	Yield (%)[a]
1	**8**	 **21**	83
2	**9**	 **22**	55[b]
3	**10**	 **23**	55[b]
4	**11**	 **24**	52[b][c]
5	**12**	 **25**	19[c]
6	**13**	 **26**	67
7	**14**	 **27**	54
8	**13**	 **28**	24[c]

Table 2. *(Continued)*

Entry	Alkyne	Product	Yield (%)[a]
9	**15**	 **29**	64[b]
10	**16**	 **30**	75
11	**17**	 **31**	69
12	**18**	 **32**	61
13	**18**	 **33**	52
14	**19**	 **34**	62[b]
15	**20**	 **35**	87

[a] Reaction conditions: a) alkyne (2.0 mmol), amine (2.0 mmol), Cp_2TiMe_2 in toluene (c = 0.37 mol/L, 0.1 mmol, 5.0 mol %), 110 °C, 12−15 h; b) $NaBH_3CN$ (4.0 mmol), $ZnCl_2{\cdot}Et_2O$ (c = 1.0 mol/L, 2.0 mmol), THF, 25 °C, 6 h. [b] 6.0 mmol of amine was used for the hydroamination step. [c] The hydroamination did not reach complete conversion; after a reaction time of 72 h, the mixture was reduced.

Conclusion

In summary, the three-step process reported, starting from easily available aryl halides, terminal alkynes, and

primary amines, represents a new and highly flexible method for the synthesis of a wide variety of biologically interesting 2-arylethylamine derivatives, and application of this new method for the generation of libraries of 2-arylethylamines should therefore be possible. Since the experimental procedures are simple, and two steps can be performed as a one-pot process, use of the presented method for automated synthesis is also imaginable. The application of efficient catalytic methods for the imine reduction would further offer the possibility to synthesize the target compounds by use exclusively of catalytic reactions. For that purpose, enantioselective reduction methods will be at the center of our interest.

Experimental Section

General Remarks: All reactions were performed under argon in flame-dried Duran glassware (e.g., Schlenk tubes equipped with Teflon stopcocks). NEt_3 was distilled from CaH_2. Cp_2TiMe_2 was synthesized according to ref.[5a] Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. Yields refer to isolated yields of pure compounds as gauged by TLC and ^1H and ^{13}C NMR. All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy, and mass spectrometry (MS). New compounds were further characterized by high-resolution mass spectrometry (HRMS) or CHN elemental analysis. NMR spectra were recorded in $CDCl_3$ with a Bruker Avance 400 MHz spectrometer. All ^1H NMR spectra are reported in δ units ppm downfield from tetramethylsilane as internal standard. All ^{13}C NMR spectra are reported in δ units ppm relative to the central line of the triplet for $CDCl_3$ at δ = 77.0. IR spectra were recorded with a Bruker Vector 22 spectrometer by an attenuated total reflection (ATR) method. MS data were recorded with a Finnigan MAT 312 or a VG Autospec (EI) with an ionization potential of 70 eV. Elemental analysis were carried out with an Elementar Vario EL machine. PE: light petroleum ether, b.p. 40−60 °C.

Sonogashira Coupling. General Procedure A: CuI (77 mg, 0.4 mmol, 4.0 mol %), $(PPh_3)_2PdCl_2$ (141 mg, 0.2 mmol, 2.0 mol %), PPh_3 (105 mg, 0.4 mmol, 4.0 mol %), and NEt_3 (30 mL) were placed in a round-bottomed flask equipped with a magnetic stirring bar. After addition of the aryl halide (10.0 mmol), the mixture was stirred for 30 min at 25 °C, and the alkyne (10.0 mmol) was then added. After this had stirred at 25 °C for a further 16 h, saturated NH_4Cl solution was added. The mixture was extracted with *tert*-butyl methyl ether (3×). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by kugelrohr distillation, followed by filtration through SiO_2 (PE/EtOAc, 20:1). **General Procedure B:** 2-Bromo-1,3-thiazole (10.0 mmol) and the alkyne (10.0 mmol) were added to a mixture of $Cu(OAc)_2{\cdot}H_2O$ (100 mg, 0.5 mmol, 5.0 mol %), $(PhCN)_2PdCl_2$ (193 mg, 0.5 mmol, 5.0 mol %), PPh_3 (262 mg, 1.0 mmol, 10.0 mol %), and diisopropylamine (20 mL). The resulting mixture was stirred at 45 °C for 12 h. After addition of saturated NH_4Cl solution, the mixture was extracted with *tert*-butyl methyl ether (3×). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by kugelrohr distillation, followed by filtration through SiO_2 (PE/EtOAc, 5:1).

Alkyne 8: General Procedure A was used to synthesize alkyne **8** from 3-iodoanisole (**1**) and 1-pentyne. After purification, compound **8** (1.48 g, 8.49 mmol, 85%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.3 Hz, 3 H), 1.62 (sext, *J* = 7.1 Hz, 2 H), 2.38 (t, *J* = 7.0 Hz, 2 H), 3.78 (s, 3 H), 6.82 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1 H), 6.93 (dd, *J* = 2.6, 1.5 Hz, 1 H), 6.99 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.18 (br. t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.4 (CH_2), 22.2 (CH_2), 55.2 (CH_3), 80.6 (C), 90.1 (C), 114.1 (CH), 116.4 (CH), 124.1 (CH), 125.1 (C), 129.2 (CH), 159.3 (C). IR: $\tilde{\nu}$ = 2962, 2934, 2904, 2872, 2835, 2229, 1599, 1576, 1481, 1464, 1427, 1316, 1287, 1268, 1205, 1175, 1164, 1044, 983, 872, 835, 777, 687 cm^{-1}. MS (25 °C): *m/z* (%) = 174 (100) [M^+], 159 (19), 145 (85), 128 (10), 115 (21), 102 (17), 91 (7), 77 (5). HRMS: calcd. ($C_{12}H_{14}O$) 174.1045; found 174.1043.

Alkyne 9: General Procedure A was used to synthesize alkyne **9** from 3-iodoanisole (**1**) and cyclopropylacetylene (70% solution in toluene). After purification, compound **9** (0.93 g, 5.41 mmol, 54%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.77−0.89 (m, 4 H), 1.39−1.48 (m, 1 H), 3.77 (s, 3 H), 6.81 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1 H), 6.90 (dd, *J* = 2.6, 1.4 Hz, 1 H), 6.97 (dt, *J* = 7.5, 1.3 Hz, 1 H), 7.16 (t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.1 (CH), 8.5 (CH_2), 55.1 (CH_3), 75.7 (C), 93.2 (C), 114.1 (CH), 116.3 (CH), 124.1 (CH), 124.9 (C), 129.1 (CH), 159.2 (C). IR: $\tilde{\nu}$ = 3009, 2957, 2834, 2226, 1596, 1573, 1481, 1464, 1426, 1314, 1284, 1269, 1209, 1163, 1040, 970, 879, 853, 810, 777, 686 cm^{-1}. MS (25 °C): *m/z* (%) = 172 (100) [M^+], 157 (12), 141 (15), 128 (27), 115 (12), 102 (6), 89 (3), 82 (6), 77 (5). HRMS: calcd. ($C_{12}H_{12}O$) 172.0888; found 172.0883. $C_{12}H_{12}O$ (172.2): calcd. C 83.69, H 7.02; found C 83.21, H 6.70.

Alkyne 10: General Procedure A was used to synthesize alkyne **10** from 1-fluoro-4-iodobenzene (**2**) and 1-pentyne. After purification, compound **10** (0.99 g, 6.10 mmol, 61%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.2 Hz, 3 H), 1.61 (sext, *J* = 7.4 Hz, 2 H), 2.36 (t, *J* = 7.0 Hz, 2 H), 6.93−7.00 (m, 2 H), 7.33−7.39 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.3 (CH_2), 22.2 (CH_2), 79.6 (C), 89.8 (C), 115.3 (CH, d, *J* = 22.0 Hz), 120.1 (C, d, *J* = 4.0 Hz), 133.3 (CH, d, *J* = 8.0 Hz), 162.0 (CF, d, *J* = 248 Hz). IR: $\tilde{\nu}$ = 2964, 2934, 2873, 2239, 1890, 1602, 1505, 1463, 1431, 1339, 1229, 1220, 1155, 1092, 1014, 833, 814 cm^{-1}. MS (25 °C): *m/z* (%) = 162 (65) [M^+], 147 (39), 133 (100), 120 (11), 107 (6). HRMS: calcd. ($C_{11}H_{11}F$) 162.0845; found 162.0842.

Alkyne 11: General Procedure A was used to synthesize alkyne **11** from 1-fluoro-4-iodobenzene (**2**) and 1-ethynylcyclohexene. After purification, compound **11** (1.34 g, 6.69 mmol, 67%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.57−1.69 (m, 4 H), 2.09−2.15 (m, 2 H), 2.17−2.22 (m, 2 H), 6.18 (m, 1 H), 6.94−6.99 (m, 2 H), 7.35−7.40 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_2), 22.3 (CH_2), 25.7 (CH_2), 29.2 (CH_2), 85.7 (C), 90.9 (C), 115.4 (CH, d, *J* = 22.0 Hz), 119.8 (C), 120.6 (C), 133.2 (CH, d, *J* = 8.0 Hz), 135.2 (CH), 162.2 (CF, d, *J* = 248 Hz). IR: $\tilde{\nu}$ = 2929, 2859, 2203, 1599, 1504, 1435, 1228, 1155, 832 cm^{-1}, MS (25 °C): *m/z* (%) = 200 (100) [M^+], 185 (46), 172 (67), 159 (31), 146 (22), 133 (39), 109 (16), 99 (8), 80 (13). HRMS: calcd. ($C_{14}H_{13}F$) 200.1001; found 200.1002.

Alkyne 12: General Procedure A was used to synthesize alkyne **12** from 1-iodo-2-(trifluoromethyl)benzene (**3**) and 1-pentyne. After purification, compound **12** (1.12 g, 5.29 mmol, 53%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.4 Hz), 1.65 (sext, *J* = 7.2 Hz, 2 H), 2.42 (t, *J* = 6.9 Hz, 2 H), 7.33 (t, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.52 (d, *J* = 7.7 Hz, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (100.6 MHz,

DEPT, $CDCl_3$): δ = 13.4 (CH_3), 21.6 (CH_2), 21.9 (CH_2), 76.9 (C), 96.6 (C), 123.7 (CF_3, q, J = 273 Hz), 125.7 (CH, q, J = 5.0 Hz), 127.1 (CH), 127.6 (C, q, J = 5.0 Hz), 131.2 (CH), 131.6 (C, q, J = 30.0 Hz), 133.9 (CH). IR: ṽ = 2966, 2036, 2874, 2238, 1604, 1573, 1450, 1315, 1167, 1131, 1110, 1062, 1033, 762 cm^{-1}. MS (25 °C): *m/z* (%) = 212 (100) [M^+], 193 (13) [M^+ − F], 183 (98), 164 (46), 145 (16), 143 (78), 115 (15), 69 (4), 67 (10). HRMS: calcd. ($C_{12}H_{11}F_3$) 212.0813; found 212.0814.

Alkyne 13: General Procedure A was used to synthesize alkyne **13** from 2-bromopyridine (**4**) and 1-pentyne. After purification, compound **13** (1.45 g, 9.98 mmol, 100%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.3 Hz, 3 H), 1.62 (sext, J = 7.3 Hz, 2 H), 2.38 (t, J = 7.2 Hz, 2 H), 7.13 (ddd, J = 7.8, 4.9, 1.1 Hz, 1 H), 7.33 (dt, J = 7.8, 1.1 Hz, 1 H), 7.57 (td, J = 7.8, 1.9 Hz, 1 H), 8.50 (ddd, J = 4.9, 1.9, 1.0 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.2 (CH_2), 21.7 (CH_2), 80.3 (C), 90.9 (C), 122.1 (CH), 126.6 (CH), 135.9 (CH), 143.8 (C), 149.6 (CH). IR: ṽ = 3051, 2963, 2933, 2872, 2222, 1581, 1561, 1462, 1427, 1380, 1339, 1268, 1227, 1148, 1091, 1043, 991, 881, 777, 739, 709 cm^{-1}. MS (25 °C): *m/z* (%) = 145 (43) [M^+], 130 (61), 117 (100), 103 (9), 89 (22), 78 (7). HRMS: calcd. ($C_{10}H_{11}N$) 145.0891; found 145.0888.

Alkyne 14: General Procedure A was used to synthesize alkyne **14** from 2-bromopyridine (**4**) and cyclopropylacetylene. After purification, compound **14** (1.42 g, 9.89 mmol, 99%) was isolated as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81−0.85 (m, 4 H), 1.37−1.45 (m, 1 H), 7.10 (ddd, J = 7.7, 5.0, 1.3 Hz, 1 H), 7.28 (dt, J = 7.9, 1.1 Hz, 1 H), 7.53 (td, J = 7.8, 1.9 Hz, 1 H), 8.45 (br. d, J = 4.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH), 8.7 (CH_2), 75.4 (C), 94.3 (C), 122.1 (CH), 126.7 (CH), 136.0 (CH), 143.7 (C), 149.6 (CH). IR: ṽ = 3046, 3007, 2220, 1578, 1559, 1464, 1427, 1358, 1283, 1269, 1235, 1180, 1150, 1059, 1036, 990, 959, 837, 820, 779, 746, 700 cm^{-1}. MS (25 °C): *m/z* (%) = 143 (100) [M^+], 130 (10), 117 (67), 115 (20), 89 (12), 78 (11). HRMS: calcd. ($C_{10}H_9N$) 143.0735; found 143.0737.

Alkyne 15: General Procedure A was used to synthesize alkyne **15** from 2-iodothiophene (**5**) and 1-pentyne. After purification, compound **15** (1.27 g, 8.42 mmol, 84%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.1 Hz, 3 H), 1.62 (sext, J = 7.1 Hz, 2 H), 2.40 (t, J = 7.1 Hz, 2 H), 6.92 (dd, J = 5.2, 3.6 Hz, 1 H), 7.11 (br. d, J = 3.6 Hz, 1 H), 7.15 (dd, J = 5.2, 1.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.6 (CH_2), 22.0 (CH_2), 73.8 (C), 94.3 (C), 124.2 (C), 125.8 (CH), 126.7 (CH), 130.8 (CH). IR: ṽ = 3106, 2963, 2933, 2872, 2833, 2224, 2156, 1599, 1519, 1493, 1454, 1427, 1380, 1338, 1277, 1238, 1190, 1046, 848, 829, 773, 697 cm^{-1}. MS (25 °C): *m/z* (%) = 150 (79) [M^+], 135 (19), 121 (100), 108 (9), 91 (14), 77 (17). HRMS: calcd. ($C_9H_{10}S$) 150.0503; found 150.0506.

Alkyne 16: General Procedure A was used to synthesize alkyne **16** from 2-iodothiophene (**5**) and cyclopropylacetylene. After purification, compound **16** (1.48 g, 9.98 mmol, 100%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78−0.90 (m, 4 H), 1.42−1.50 (m, 1 H), 6.91 (dd, J = 5.2, 3.6 Hz, 1 H), 7.09 (dd, J = 3.6, 1.1 Hz, 1 H), 7.14 (dd, J = 5.2, 1.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.3 (CH), 8.7 (CH_2), 68.8 (C), 97.4 (C), 124.1 (C), 125.9 (CH), 126.7 (CH), 131.1 (CH). IR: ṽ = 3092, 3012, 2222, 1798, 1520, 1428, 1366, 1339, 1243, 1205, 1174, 1088, 1053, 1040, 1028, 931, 850, 828, 810, 697 cm^{-1}. MS (25 °C): *m/z* (%) = 148 (100) [M^+], 147 (97), 121 (13), 120 (12), 115 (35), 77 (7). HRMS: calcd. (C_9H_8S) 148.0347; found 148.0344.

Alkyne 17: General Procedure B was used to synthesize alkyne **17** from 2-bromo-1,3-thiazole (**6**) and 1-pentyne. After purification, compound **17** (0.82 g, 5.43 mmol, 54%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.4 Hz, 3 H), 1.64 (sext, J = 7.3 Hz, 2 H), 2.41 (t, J = 7.2 Hz, 2 H), 7.24 (d, J = 3.4 Hz, 1 H), 7.73 (d, J = 3.4 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.4 (CH_2), 21.5 (CH_2), 74.1 (C), 96.2 (C), 119.7 (CH), 142.9 (CH), 149.4 (C). IR: ṽ = 3115, 3082, 2963, 2934, 2872, 2229, 1479, 1463, 1411, 1338, 1321, 1275, 1244, 1215, 1130, 1046, 950, 929, 870, 777, 756, 721, 688 cm^{-1}. MS (25 °C): *m/z* (%) = 151 (100) [M^+], 136 (54), 122 (55), 109 (11), 78 (9). HRMS: calcd. (C_8H_9NS) 151.0456; found 151.0453. C_8H_9NS (151.2): calcd. C 63.54, H 6.00, N 9.26; found C 63.82, H 5.92, N 9.31.

Alkyne 18: General Procedure B was used to synthesize alkyne **18** from 2-bromo-1,3-thiazole (**6**) and cyclopropylacetylene. After purification, compound **18** (0.94 g, 6.32 mmol, 63%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88−0.96 (m, 4 H), 1.46−1.54 (m, 1 H), 7.25 (d, J = 3.3 Hz, 1 H), 7.73 (d, J = 3.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.1 (CH), 8.8 (CH_2), 69.0 (C), 99.3 (C), 119.6 (CH), 142.8 (CH), 149.3 (C). IR: ṽ = 3114, 3082, 3010, 2222, 1480, 1451, 1420, 1380, 1345, 1317, 1244, 1225, 1180, 1138, 1084, 1053, 1030, 936, 873, 813, 777, 721, 688 cm^{-1}. MS (25 °C): *m/z* (%) = 149 (100) [M^+], 136 (38), 122 (44), 109 (10), 104 (34), 78 (10), 77 (10), 76 (15), 69 (10). HRMS: calcd. (C_8H_7NS) 149.0299; found 149.0299.

Alkyne 19: General Procedure A was used to synthesize alkyne **19** from 2-iodofuran (**7**) and 1-pentyne. After purification, compound **19** (0.60 g, 4.46 mmol, 45%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.1 Hz, 3 H), 1.60 (sext, J = 7.0 Hz, 2 H), 2.39 (t, J = 7.0 Hz, 2 H), 6.32 (dd, J = 3.4, 2.0 Hz, 1 H), 6.44 (br. d, J = 3.4 Hz, 1 H), 7.30 (dd, J = 1.9, 0.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.5 (CH_3), 21.4 (CH_2), 21.8 (CH_2), 71.0 (C), 94.6 (C), 110.6 (CH), 113.6 (CH), 137.6 (C), 142.6 (CH). IR: ṽ = 2964, 2934, 2873, 2238, 1573, 1487, 1461, 1428, 1376, 1339, 1326, 1277, 1250, 1209, 1154, 1076, 1015, 984, 966, 901, 885, 809, 774, 735, 654, 592 cm^{-1}. MS (25 °C): *m/z* (%) = 134 (100) [M^+], 119 (6), 105 (91), 91 (31), 77 (68). HRMS: calcd. ($C_9H_{10}O$) 134.0732; found 134.0735.

Alkyne 20: General Procedure A was used to synthesize alkyne **20** from 2-iodofuran (**7**) and 1-ethynylcyclohexene. After purification, compound **20** (1.39 g, 8.09 mmol, 81%) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55−1.70 (m, 4 H), 2.10−2.16 (m, 2 H), 2.17−2.23 (m, 2 H), 6.21−6.26 (m, 1 H), 6.37 (dd, J = 3.4, 1.9 Hz, 1 H), 6.52 (dd, J = 3.4, 0.8 Hz, 1 H), 7.36 (dd, J = 1.9, 0.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 21.4 (CH_2), 22.2 (CH_2), 25.7 (CH_2), 28.7 (CH_2), 76.7 (C), 95.0 (C), 110.9 (CH), 114.3 (CH), 119.9 (C), 136.2 (CH), 137.5 (C), 143.1 (CH). IR: ṽ = 2930, 2859, 2203, 1570, 1485, 1435, 1348, 1279, 1259, 1211, 1157, 1075, 1011, 965, 918, 885, 841, 800, 735 cm^{-1}. MS (25 °C): *m/z* (%) = 172 (100) [M^+], 157 (6), 144 (20), 128 (19), 115 (22), 105 (3), 103 (3), 89 (5). HRMS: calcd. ($C_{12}H_{12}O$) 172.0888; found 172.0888.

Hydroamination/Reduction. General Procedure: A Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with amine (2.0 mmol), alkyne (2.0 mmol), and a solution of Cp_2TiMe_2 (0.27 mL, 0.37 mol/L in toluene, 0.1 mmol, 5.0 mol %). The mixture was heated to 110 °C for 12−15 h (TLC monitoring). The obtained brown liquid was dissolved in THF (6.0 mL) and added to a mixture of $NaBH_3CN$ (251 mg, 4.0 mmol) and $ZnCl_2{\cdot}Et_2O$ (2.0 mL, 1.0 mol/L in Et_2O, 2.0 mmol) in THF (4.0 mL). After this had stirred at 25 °C for 6 h, 2 N HCl was added and the mixture was extracted with EtOAc (2×). KOH (2 N) was

added to the aqueous layer until pH = 12 was reached. The basic aqueous layer was extracted with EtOAc (2×). The combined organic layers were extracted with 2 N KOH and brine. After drying with Na_2SO_4 and concentration under vacuum, the residue was purified by flash chromatography (SiO_2).

Amine 21: The General Procedure was used to synthesize amine **21** from 4-methoxyaniline and acetylene **8**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 5:1), compound **21** (497 mg, 1.66 mmol, 83%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.30−1.52 (m, 4 H), 2.74 (dd, *J* = 13.6, 6.5 Hz, 1 H), 2.81 (dd, *J* = 13.6, 4.8 Hz, 1 H), 3.52−3.58 (m, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 6.55−6.59 (m, 2 H), 6.69−6.70 (m, 1 H), 6.74−6.80 (m, 4 H), 7.19 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.1 (CH_3), 19.3 (CH_2), 36.3 (CH_2), 40.1 (CH_2), 54.3 (CH), 55.1 (CH_3), 55.8 (CH_3), 111.3 (CH), 114.6 (CH), 115.0 (CH), 115.4 (CH), 122.0 (CH), 129.1 (CH), 140.3 (C), 141.9 (C), 151.8 (C), 159.5 (C). IR: ṽ = 3391, 2932, 2832, 1600, 1583, 1509, 1235, 1039, 817, 736 cm^{-1}. MS (80 °C): *m*/*z* (%) = 299 (33) [M$^+$], 178 (100), 149 (16), 122 (14), 91 (6). HRMS: calcd. ($C_{19}H_{25}NO_2$) 299.1885; found 299.1887. $C_{19}H_{25}NO_2$ (299.4): calcd. C 76.22, H 8.42, N 4.68; found. C 76.54, H 8.22, N 4.62.

Amine 22: The General Procedure was used to synthesize amine **22** from *tert*-butylamine and acetylene **9** (6.0 mmol of amine was used). After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 3:1), compound **22** (271 mg, 1.10 mmol, 55%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.07−0.14 (m, 2 H), 0.31−0.43 (m, 2 H), 0.67−0.76 (m, 1 H), 1.04 (s, 9 H), 2.14−2.19 (m, 1 H), 2.73 (dd, *J* = 13.2, 7.0 Hz, 1 H), 2.80 (dd, *J* = 13.2, 5.8 Hz, 1 H), 3.77 (s, 3 H), 6.71−6.79 (m, 3 H), 7.16 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 4.3 (CH_2), 4.7 (CH_2), 18.1 (CH), 30.2 (CH_3), 44.9 (CH_2), 50.4 (C), 55.1 (CH_3), 58.0 (CH), 111.1 (CH), 115.5 (CH), 122.1 (CH), 128.9 (CH), 144.5 (C), 151.4 (C). IR: ṽ = 3076, 2998, 2957, 2866, 1601, 1584, 1487, 1454, 1362, 1258, 1152, 1045, 775, 696 cm^{-1}. MS (25 °C): *m*/*z* (%) = 232 (15) [M$^+$ − CH_3], 192 (39), 166 (29), 136 (38), 126 (99), 121 (38), 110 (31), 91 (26), 70 (100). HRMS: calcd. ($C_{16}H_{25}NO$) 247.1936; found 247.1914.

Amine 23: The General Procedure was used to synthesize amine **23** from *tert*-butylamine and acetylene **10** (6.0 mmol of amine was used). After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 1:1), compound **23** (263 mg, 1.11 mmol, 55%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.00 (s, 9 H), 1.27−1.45 (m, 4 H), 2.57 (dd, *J* = 13.5, 6.5 Hz, 1 H), 2.64 (dd, *J* = 13.5, 6.6 Hz, 1 H), 2.75 (m, 1 H), 6.96 (m, 2 H), 7.14 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.3 (CH_3), 19.4 (CH_2), 30.0 (CH_3), 39.2 (CH_2), 43.1 (CH_2), 50.8 (C), 53.5 (CH), 114.8 (CH, d, *J* = 21.0 Hz), 130.7 (CH, d, *J* = 8.0 Hz), 135.9 (C, d, *J* = 3.0 Hz), 161.4 (CF, d, *J* = 242 Hz). IR: ṽ = 3039, 2957, 2930, 2870, 1601, 1508, 1361, 1221, 818 cm^{-1}. MS (25 °C): *m*/*z* (%) = 236 (1) [M$^+$ − 1], 222 (23), 194 (11), 128 (72), 109 (44), 72 (100). HRMS: calcd. ($C_{15}H_{23}FN$) 236.1815; found 236.1800.

Amine 24: The General Procedure was used to synthesize amine **24** from *tert*-butylamine and acetylene **11** (6.0 mmol of amine was used). The reaction time for the hydroamination step was 72 h. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 3:1), compound **24** (286 mg, 1.04 mmol, 52%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 9 H), 1.47−1.63 (m, 4 H), 1.91−2.00 (m, 4 H), 2.58 (dd, *J* = 13.3, 8.2 Hz, 1 H), 2.69 (dd, *J* = 13.3, 6.4 Hz, 1 H), 3.30−3.34 (m, 1 H), 5.48 (m, 1 H), 6.93−6.98 (m, 2 H), 7.10−7.14 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 22.8 (CH_2), 24.2 (CH_2), 25.2 (CH_2), 29.6 (CH_3), 42.3 (CH_2), 51.0 (C), 61.5 (CH), 114.8 (CH, d, *J* = 21.0 Hz), 122.9 (CH), 130.5 (CH, d, *J* = 8.0 Hz), 135.5 (C, d, *J* = 3.0 Hz), 140.9 (C), 161.4 (CF, d, *J* = 244 Hz). IR: ṽ = 3040, 2925, 2856, 2414, 1601, 1508, 1447, 1361, 1221, 1157, 822 cm^{-1}. MS (25 °C): *m*/*z* (%) = 275 (2) [M$^+$], 260 (3) [M$^+$ − CH_3], 180 (7), 166 (83), 138 (19), 110 (100), 93 (30), 81 (18), 77 (14). HRMS: calcd. ($C_{18}H_{26}FN$) 275.2049; found 275.2048.

Amine 25: The General Procedure was used to synthesize amine **25** from 4-methoxyaniline and acetylene **12**. The reaction time for the hydroamination step was 72 h. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 3:1), compound **25** (130 mg, 0.39 mmol, 19%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 1.34−1.50 (m, 4 H), 2.94 (br. s, 1 H), 2.96 (br. s, 1 H), 3.62 (quint, *J* = 6.4 Hz, 1 H), 3.71 (s, 3 H), 6.44−6.48 (m, 2 H), 6.69−6.73 (m, 2 H), 7.24−7.28 (m, 1 H), 7.38−7.43 (m, 2 H), 7.60−7.66 (m, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.0 (CH_3), 19.2 (CH_2), 37.6 (CH_2), 38.2 (CH_2), 55.2 (CH), 55.8 (CH_3), 114.4 (CH), 114.9 (CH), 124.7 (CF_3, q, *J* = 274 Hz), 126.0 (CH, q, *J* = 6.0 Hz), 126.1 (CH), 128.9 (C, q, *J* = 29.0 Hz), 131.5 (CH), 131.5 (CH, q, *J* = 1.0 Hz), 138.3 (C, q, *J* = 2.0 Hz), 142.0 (C), 151.8 (C). IR: ṽ = 3389, 2957, 2933, 1607, 1509, 1455, 1311, 1237, 1113, 1035, 816, 765. MS (100 °C): *m*/*z* (%) = 337 (18) [M$^+$], 294 (4), 178 (100), 159 (13), 134 (12), 109 (7), 92 (3). HRMS: calcd. ($C_{19}H_{22}F_3NO$) 337.1653; found 337.1657.

Amine 26: The General Procedure was used to synthesize amine **26** from 4-methoxyaniline and acetylene **13**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 1:1), compound **26** (362 mg, 1.34 mmol, 67%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.37−1.52 (m, 4 H), 2.93 (dd, *J* = 13.4, 5.8 Hz, 1 H), 2.98 (dd, *J* = 13.4, 6.2 Hz, 1 H), 3.68−3.71 (m, 1 H), 3.72 (s, 3 H), 6.55−6.59 (m, 2 H), 6.72−6.76 (m, 2 H), 7.07−7.13 (m, 2 H), 7.54 (dt, *J* = 7.7, 1.9 Hz, 1 H), 8.54 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT,$CDCl_3$): δ = 14.1 (CH_3), 19.2 (CH_2), 37.0 (CH_2), 42.9 (CH_2), 54.4 (CH), 55.8 (CH_3), 114.6 (CH), 114.9 (CH), 121.1 (CH), 123.8 (CH), 136.1 (CH), 142.1 (C), 149.2 (CH), 151.7 (C), 159.7 (C). IR: ṽ = 3351, 2954, 2930, 1617, 1568, 1509, 1466, 1434, 1234, 1038, 817, 749 cm^{-1}. MS (60 °C): *m*/*z* (%) = 270 (67) [M$^+$], 227 (54), 178 (100), 134 (20), 93 (63). HRMS: calcd. ($C_{17}H_{22}N_2O$) 270.1732; found 270.1736. $C_{17}H_{22}N_2O$ (270.4): calcd. C 75.52, H 8.20, N 10.36; found C 75.89, H 8.15, N 10.31.

Amine 27: The General Procedure was used to synthesize amine **27** from benzhydrylamine and acetylene **14**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 1:1), compound **27** (354 mg, 1.08 mmol, 54%) was isolated as a colorless oil.^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.14−(−0.08) (m, 1 H), 0.12−0.18 (m, 1 H), 0.29−0.36 (m, 1 H), 0.50−0.57 (m, 1 H), 0.74−0.83 (m, 1 H), 2.14−2.20 (m, 2 H), 2.97 (dd, *J* = 13.3, 8.0 Hz, 1 H), 3.10 (dd, *J* = 13.3, 4.8 Hz, 1 H), 5.18 (s, 1 H), 7.08−7.33 (m, 12 H), 7.56 (dt, *J* = 7.6, 1.9 Hz, 1 H), 8.53 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 1.6 (CH_2), 5.0 (CH_2), 16.6 (CH), 44.5 (CH_2), 60.4 (CH), 63.7 (CH), 121.0 (CH), 124.1 (CH), 126.5 (CH), 126.7 (CH), 127.3 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 135.9 (CH), 143.9 (C), 144.9 (C), 149.0 (CH), 160.2 (C). IR: ṽ = 3306, 3061, 3024, 3001, 2919, 1737, 1589, 1568, 1492, 1474, 1452, 1434, 1101, 1076, 1049, 1026, 744, 697 cm^{-1}. MS (80 °C): *m*/*z* (%) = 329 (17) [M$^+$ + 1],

301 (11), 236 (43), 207 (28), 182 (93), 167 (100), 152 (40), 117 (28), 104 (24), 93 (33), 77 (17). HRMS: calcd. ($C_{23}H_{24}N_2$) 328.1939; found 328.1936.

Amine 28: The General Procedure was used to synthesize amine **28** from benzylamine and acetylene **13**. The reaction time for the hydroamination step was 72 h. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 1:3), compound **28** (124 mg, 0.49 mmol, 24%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.0 Hz, 3 H), 1.28−1.45 (m, 4 H), 2.81 (dd, *J* = 13.6, 7.4 Hz), 2.84 (dd, *J* = 13.6, 5.5 Hz, 1 H), 2.93−2.99 (m, 1 H), 3.63−3.74 (m, 2 H), 7.03−7.21 (m, 7 H), 7.50 (dt, *J* = 7.6, 1.9 Hz, 1 H), 8.47 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.3 (CH_3), 19.0 (CH_2), 36.6 (CH_2), 43.0 (CH_2), 51.2 (CH_2), 57.4 (CH), 121.1 (CH), 123.9 (CH), 126.7 (CH), 128.0 (CH), 128.2 (CH), 136.1 (CH), 140.9 (C), 149.2 (CH), 160.3 (C). IR: ṽ = 3306, 3061, 3026, 2955, 2928, 2870, 1589, 1568, 1472, 1453, 1433, 1376, 1345, 1136, 746, 697 cm^{-1}. MS (25 °C): *m*/*z* (%) = 254 (1) [M$^+$], 211 (41), 162 (65), 149 (45), 132 (15), 120 (36), 106 (40), 91 (100), 65 (27). HRMS: calcd. ($C_{17}H_{22}N_2$) 254.1783; found 254.1783.

Amine 29: The General Procedure was used to synthesize amine **29** from *tert*-butylamine and acetylene **15** (6.0 mmol of amine was used). After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 5:1), compound **29** (288 mg, 1.28 mmol, 64%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.6 Hz, 3 H), 1.04 (s, 9 H), 1.26−1.40 (m, 4 H), 2.76−2.81 (m, 1 H), 2.84−2.90 (m, 2 H), 6.82 (dd, *J* = 3.4, 1.2 Hz, 1 H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1 H), 7.15 (dd, *J* = 5.1, 1.2 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.2 (CH_3), 19.5 (CH_2), 30.0 (CH_3), 38.0 (CH_2), 38.9 (CH_2), 50.9 (C), 53.3 (CH), 123.5 (CH), 125.5 (CH), 126.4 (CH), 142.3 (C). IR: ṽ = 3069, 2956, 2929, 2820, 1438, 1361, 689 cm^{-1}. MS (25 °C): *m*/*z* (%) = 210 (2) [M$^+$ − CH_3], 128 (63), 97 (24), 72 (100). HRMS: calcd. ($C_{12}H_{20}NS$) 210.1316; found 210.1316.

Amine 30: The General Procedure was used to synthesize amine **30** from benzhydrylamine and acetylene **16**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 10:1), compound **30** (498 mg, 1.49 mmol, 75%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.04−0.00 (m, 1 H), 0.11−0.17 (m, 1 H), 0.36−0.43 (m, 1 H), 0.51−0.57 (m, 1 H), 0.70−0.79 (m, 1 H), 1.87 (br. s, 1 H), 1.93−1.98 (m, 1 H), 2.99 (dd, *J* = 14.6, 7.2 Hz, 1 H), 3.13 (ddd, *J* = 14.6, 4.2, 0.4 Hz, 1 H), 5.18 (s, 1 H), 6.83 (dd, *J* = 3.4, 1.0 Hz, 1 H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1 H), 7.14−7.29 (m, 9 H), 7.33−7.35 (m, 2 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 1.7 (CH_2), 5.0 (CH_2), 16.0 (CH), 35.8 (CH_2), 60.7 (CH), 63.7 (CH), 123.8 (CH), 126.0 (CH), 126.6 (CH), 126.7 (CH), 126.8 (CH), 127.3 (CH), 127.4 (CH), 128.3 (CH), 128.4 (CH), 141.4 (C), 143.8 (C), 144.6 (C). IR: ṽ = 3062, 3024, 3000, 2914, 1598, 1492, 1452, 1130, 1020, 744, 693 cm^{-1}. MS (25 °C): *m*/*z* (%) = 236 (56), 167 (100), 152 (29), 97 (24). HRMS: calcd. ($C_{22}H_{23}NS$) 333.1551; found 333.1504.

Amine 31: The General Procedure was used to synthesize amine **31** from 4-methylaniline and acetylene **17**. Prior to use, 4-methylaniline was purified by kugelrohr distillation. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 5:1), compound **31** (360 mg, 1.38 mmol, 69%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H), 1.37−1.56 (m, 4 H), 2.22 (s, 3 H), 3.19 (dd, *J* = 14.7, 5.6 Hz, 1 H), 3.23 (dd, *J* = 14.7, 5.5 Hz, 1 H), 3.76 (m, 1 H), 6.56 (m, 2 H), 6.98 (m, 2 H), 7.17 (d, *J* = 3.4 Hz, 1 H), 7.70 (d, *J* = 3.4 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.0 (CH_3), 19.3 (CH_2), 20.3 (CH_3), 36.8 (CH_2), 37.6 (CH_2), 53.3 (CH), 113.5 (CH), 118.5 (CH), 126.5 (C), 129.8 (CH), 142.2 (CH), 144.9 (C), 167.5 (C). IR: ṽ = 3298, 3020, 2953, 2928, 2858, 1616, 1520, 1496, 1130, 1051, 973, 814, 718 cm^{-1}. MS (25 °C): *m*/*z* (%) = 260 (24) [M$^+$], 217 (10), 162 (100), 120 (10), 91 (11). HRMS: calcd. ($C_{15}H_{20}N_2S$) 260.1347; found 260.1346. $C_{15}H_{20}N_2S$ (260.4): calcd. C 69.19, H 7.73, N 10.76; found C 69.11, H 7.62, N 10.56.

Amine 32: The General Procedure was used to synthesize amine **32** from 4-methoxyaniline and acetylene **18**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 3:1), compound **32** (335 mg, 1.22 mmol, 61%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14−0.18 (m, 1 H), 0.26−0.33 (m, 1 H), 0.42−0.51 (m, 2 H), 0.85−0.92 (m, 1 H), 3.12 (dt, *J* = 8.0, 5.6 Hz, 1 H), 3.31 (d, *J* = 5.6 Hz, 2 H), 3.74 (s, 3 H), 6.61−6.66 (m, 2 H), 6.73−6.77 (m, 2 H), 7.21 (d, *J* = 3.3 Hz, 1 H), 7.74 (d, *J* = 3.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 3.1 (CH_2), 3.3 (CH_2), 16.1 (CH), 38.2 (CH_2), 55.7 (CH_3), 58.9 (CH), 114.8 (CH), 114.8 (CH), 116.4 (CH), 141.5 (C), 142.5 (CH), 157.3 (C), 167.5 (C). IR: ṽ = 3350, 2999, 2933, 1508, 1233, 819 cm^{-1}. MS (90 °C): *m*/*z* (%) = 274 (34) [M$^+$], 175 (100), 145 (10), 123 (22), 108 (21), 99 (8). HRMS: calcd. ($C_{15}H_{18}N_2OS$) 274.1140; found 274.1137.

Amine 33: The General Procedure was used to synthesize amine **33** from benzhydrylamine and acetylene **18**. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 10:1), compound **33** (347 mg, 1.04 mmol, 52%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.07−0.00 (m, 1 H), 0.12−0.18 (m, 1 H), 0.36−0.43 (m, 1 H), 0.52−0.59 (m, 1 H), 0.74−0.83 (m, 1 H), 2.12−2.17 (m, 1 H), 3.20 (dd, *J* = 14.6, 7.2 Hz, 1 H), 3.31 (dd, *J* = 14.6, 4.5 Hz, 1 H), 5.20 (s, 1 H), 7.13−7.38 (m, 11 H), 7.71 (d, *J* = 3.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 1.8 (CH_2), 5.1 (CH_2), 16.1 (CH), 39.0 (CH_2), 60.1 (CH), 63.9 (CH), 118.6 (CH), 126.7 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 128.0 (CH), 128.3 (CH), 142.0 (CH), 143.7 (C), 144.5 (C), 168.1 (C). IR: ṽ = 3309, 3024, 2847, 1598, 1493, 1452, 1427, 1125, 1050, 1024, 920, 744, 697 cm^{-1}. MS (90 °C): *m*/*z* (%) = 335 (1) [M$^+$ + 1], 236 (50), 210 (14), 182 (64), 167 (100), 152 (44), 103 (20). HRMS: calcd. ($C_{21}H_{22}N_2S$) 334.1504; found 334.1482.

Amine 34: The General Procedure was used to synthesize amine **34** from *tert*-butylamine and acetylene **19** (6.0 mmol of amine was used). After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 1:1), compound **34** (260 mg, 1.24 mmol, 62%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84−0.88 (m, 3 H), 0.99 (s, 9 H), 1.22−1.39 (m, 4 H), 2.59 (dd, *J* = 14.7, 6.4 Hz, 1 H), 2.68 (dd, *J* = 14.8, 6.4 Hz, 1 H), 2.80−2.85 (m, 1 H), 6.00 (dd, *J* = 3.1, 0.8 Hz, 1 H), 6.24 (dd, *J* = 3.1, 1.8 Hz, 1 H), 7.28 (dd, *J* = 1.8, 0.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 14.3 (CH_3), 19.4 (CH_2), 29.9 (CH_3), 36.1 (CH_2), 39.9 (CH_2), 51.0 (C), 51.2 (CH), 106.7 (CH), 110.1 (CH), 141.0 (CH), 154.2 (C). IR: ṽ = 3113, 2957, 2931, 2871, 1464, 1387, 1362, 1229, 1146, 1009, 925, 797, 724 cm^{-1}. MS (25 °C): *m*/*z* (%) = 209 (1) [M$^+$], 194 (11), 152 (11), 128 (70), 110 (27), 96 (12), 81 (43), 72 (100). HRMS: calcd. ($C_{13}H_{23}NO$) 209.1780; found 209.1751.

Amine 35: The General Procedure was used to synthesize amine **35** from 4-methylaniline and acetylene **20**. Prior to use, 4-methylaniline was purified by kugelrohr distillation. After reduction with $NaBH_3CN$ and purification by flash chromatography (PE/EtOAc, 5:1), compound **35** (490 mg, 1.74 mmol, 87%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51−1.65 (m, 4 H), 1.94−2.00 (m, 4 H), 2.20 (s, 3 H), 2.89 (dd, *J* = 15.1, 7.7 Hz,

1 H), 2.94 (dd, J = 15.1, 5.7 Hz, 1 H), 3.89−3.92 (m, 1 H), 5.66−5.71 (m, 1 H), 6.07 (dd, J = 3.1, 0.8 Hz, 1 H), 6.28 (dd, J = 3.1, 1.9 Hz, 1 H), 6.48−6.54 (m, 2 H), 6.93−6.96 (m, 2 H), 7.31 (dd, J = 1.8, 0.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 20.3 (CH_3), 22.6 (CH_2), 22.8 (CH_2), 24.5 (CH_2), 25.0 (CH_2), 37.7 (CH_2), 59.2 (CH), 106.8 (CH), 110.2 (CH), 113.5 (CH), 123.2 (CH), 126.2 (C), 129.5 (CH), 137.7 (C), 141.4 (CH), 145.5 (C), 153.0 (C). IR: $\tilde{\nu}$ = 3408, 3016, 2922, 2856, 2835, 1616, 1518, 1485, 1447, 1436, 804, 726 cm^{-1}. MS (25 °C): m/z (%) = 281 (4) [M^+], 200 (100), 186 (11), 139 (16), 137 (16), 91 (12). HRMS: calcd. ($C_{19}H_{23}NO$) 281.1780; found 281.1776.

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