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Synthesis of *N*-alkyl-*N′*-aryl or Alkenylpiperazines: A Copper-catalyzed C-N Cross-coupling in the Presence of Aryl and Alkenyl Triflates and DABCO

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Unsymmetrical piperazines are key constituents of many pharmaceuticals. Given that the selective introduction of an aryl and alkyl motif onto the piperazine is not always straightforward, direct arylation and alkenylation of 1,4-diaza-bicyclo[2.2.2]octane would obviate the inefficiencies associated with the preparation of these target molecules. We have utilized alkyl halides, aryl or alkenyl triflates, and 1,4-diaza-bicyclo[2.2.2]octane for the synthesis of *N*-alkyl-*N′*-aryl or alkenylpiperazines. The optimum conditions are developed using CuCl, *t*-BuOLi in NMP. Alkenyl triflates requires *N*, *N′*-dimethyl ethylenediamine and higher temperature to afford the desired cross-coupled product. Substrates bearing electron-deficient and electron-rich groups were successfully coupled under the optimum reaction conditions.

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Introduction. - The ability to selectively form carbon-nitrogen bond between different fragments has been crucial to the development of synthetic organic chemistry.[1-3] Over the past decades, the selective coupling of nucleophilic nitrogen with aryl sources using transition metal catalysts has almost replaced classical methods of aryl-nitrogen bond formations.[4-10] The piperazine scaffold is a common motif in pharmaceuticals and bioactive natural products.[11-12] Several piperazine-containing drugs are within the top 100 best-selling pharmaceutical products. The high value of the piperazine motif is reflected in the myriad strategies for its construction, the majority of which involve stepwise synthesis.[13-17] These studies are very well recapitulated in a review written by Dai.[18] Since the pioneering work of Ross,[19] the ring-opening of DABCO prompted by nucleophilic attack on the corresponding bicyclic quaternary ammonium salts have been well developed over the past decades.[20-26] The literature on ring-opening reactions of quinuclidine derivatives has been reviewed up to the year 1984.[27] Wang and co-workers have documented an efficient *N*-arylation/dealkylation of electron deficient heteroaryl chlorides and DABCO under microwave irradiation.[28] Peters reported the ring opening of *N*-benzylquinuclidinium bromide using a range of nucleophiles.[29] While the importance of such reports cannot be overstated,

these transformations are limited to form *N*-alkyl and/or *N*-arylpiperazines bearing strong electronic directing groups. It is worth mentioning that a decent range of the piperazine-containing small-molecule drugs have aryl- or heteroaryl substitution on either both nitrogen atoms or on a single nitrogen atom. The lack of efficient synthetic methods, particularly those that provide high selectivity for *N*-arylation of piperazines with unactivated aryl halides and use readily available starting materials, represents one of the hurdles in unleashing the full therapeutic potential of piperazines. Moreover, a facile catalytic *N*-arylation and *N*-alkenylation of DABCO with unactivated aryl haildes and alkenyl halides is still a challenge. Recently, Yavari and co-workers have developed a concise procedure for the synthesis of *N*-alkyl-*N*′-arylpiperazines from readily available DABCO, unactivatied aryl halides, and alkyl halides.[30] The ring-opening cross-coupling strategy gave *N*-alkyl-*N*′-arylpiperazines in high yields. This method is appealing because *N*-arylpiperazines could be achieved selectively from readily available DABCO and common aryl halides. Successful catalytic formation of *N*-aryl and *N*-heteroarylpiperazines using aryl and heteroaryl halides could find broad utility owing to the presence in a wide range of drugs skeletons. The problem addressed above encouraged us to examine the efficiency of aryl and alkenyl halides or triflates in a reaction involving quaternary ammonium salt of DABCO to form diverse *N*-aryl and *N*-alkenyl arylpiperazines.

In continuation of our reports in catalysis,[31-32] we describe the direct conversion of DABCO to *N*-alkyl-*N*′-arylpiperazines and *N*-alkyl-*N*′-alkenylpiperazines by the reaction with aryl or alkenyl triflates and alkyl halides catalytic in copper.

Results and Discussion. - To test our hypothesis and identify systems capable of mediating this highly desirable process, we chose as a model reaction the cross-coupling of DABCO (**1**), benzyl chloride (**2a**), and phenyl trifluoromethanesulfonate (**3a**) using copper(I) iodide and *t*-BuOK. Stirring in DMSO at 70 °C for 14 h, gave *N*-alkyl-*N*′-arylpiperazine **4a** only in 15% yield. To develop the reaction conditions, we began by screening the reaction conditions and optimizing with respect to catalyst, solvent, and base. No the desired reaction took place in the absence of a copper source even at higher temperatures (not shown in Table 1). The reaction proceeded in high yield using CuOTf and

CuCl (Table 1, entries 1 and 2). Other copper(I) salts also mediated the reaction however, the yield were unsatisfactory (Table 1, entries 3-6). Coper(II) salts were not suitable in this transformation (Table 1, entries 7-9). The choice of base source was found to influence the reaction outcome in appreciable manner: only a bulky base with lithium as the counter-cation afforded the product in high yield, indicating that strong proton abstracting character of the *t*.BuO and strong Lewis acid property of Li is crucial (Table 1, entries 2 and 3). Yavari has reported that the addition of lithium iodide increased the efficiency of aryl triflates in C-N cross-coupling reaction.[33] We believe that lithium cation participates in addition oxidation step of aryl triflate to copper salt by coordination to triflate group and hereby facilitates the reaction progress. When the reaction was conducted with *t*-BuOK at elevated temperature the desired product obtained in comparatively good yield (Table 1, entry 22). With *t*-BuOCs as the base source, phenyl trifluoromethanesulfonate (**3a**) was recovered in 90% yield and no product arising from the cross-coupling reaction is detected using GC analysis (Table 1, entry 10). ^{1}H-NMR analysis indicated that *trans*-stilbene was formed as the side product in 53% yield. It could be deduced that strongly basic *t*-BuOCs let to formation of stilbenes *via* deprotonation at the benzylic position. Moreover, the counter-cation might participate in the reaction progress beyond the acting as the Lewis acid.[1] The reaction is completely selective for cross-coupling reaction and no compounds arising from the attack on benzyne motif are detected by crude GC-MS analysis. Moreover, almost no desired reaction took place in the presence of other common inorganic bases at 70 °C (Table 1, entries 10-14). Finally, a solvent screen showed that NMP was superior to other solvents (Table 1, entries 2 and 3). The reaction proceeded in moderate yield in dimethyl acetamide (DMA) (Table 1, entry 17). Toluene and 1,4-dioxane failed to increase the yield of the desired product (Table 1, entries 19-20). Reaction conducted in ethylene glycol formed only a low yield of the desired product (Table 1, entry 21).

[1] We are grateful to a Referee of this paper for his suggestion about the formation of stilbene as the side product in the presence of *t*.BuOCs.

A wide variety of aryl triflates were reacted under the conditions for entry 2 of Table 1. Phenyl and 2-naphtyl triflates (**3a** and **3b**) were readily transformed to the desired products (Table 2, entries 1 and 2). Electron-rich aryl triflates were less reactive. The use of twice the amounts of the catalyst and 1.5 mmol of DABCO was required to convert *t*-butyl-, methyl, and methoxy-substituted triflates to the corresponding products within acceptable reaction times (Table 2, entries 3-6). Aryl triflates having an electron-withdrawing group such as acetyl, cyano, and nitro reacted in high yields (Table 2, entries 7-8 and 11-13). Heteroaryl triflates also afforded the products in good yields (Table 2, entries 9 and 10). Notably, the tolerance for the heteroaromatic ring offers an opportunity for expedient synthesis of heteroarylpiperazine-containing drugs likes Buspirone, Gepirone, Ipsapirone, Tandospirone, and Zalospirone.

This transformation was further generalized, allowing the coupling of a range of alkenyl iodides and triflates in moderate to good yields (Table 3). The use of *N*, *N*′-dimethyl ethylenediamine as ligand was required to furnish the transformation in good yields within acceptable reaction periods. Alkenyl iodides were reacted more effectively than those of alkenyl triflates. It should be noted that the reaction proceeded almost in stereoselective manner as the *Z*-isomer gives the *Z*-alkenylated product in high yield (Table 3, entry 2) and the *E*-isomers give the *E*-alkenylated products in high yields (Table 3, entries 3 and 5).

The coupling of other alkyl chlorides was also examined with the same catalyst system (Table 4). The amination of *n*-butyl and *n*-hexyl chlorides (**2b** and **2c**) was found to proceed with acceptable yields (Table 4, entries 1 and 2). Allyl chloride (**2d**) afforded the corresponding alkylated product in good yield (Table 4, entry 3). Steric hindrance of the substrates adversely affected the reaction progress, as 1-chloro-2-methylpropane (**2e**) and 2-chloropropane (**2f**) gave the desired products in moderate yields (Table 4, entries 5 and 6). It is important to stop the reaction at the time indicated; extended heating resulted in decomposition of the products probably due to the Hofmann type

elimination. Reaction conducted with 1,2-dichloroethane resulted in formation of a complicated reaction mixture (not shown in Table 4).

To show the advantages and disadvantages of the proposed method we provide a comparison with the pervious reported methods. In 2007, Wolfe and co-workers reported a 2,6-disubstituted *N*-alkyl-*N*′-arylpiperazines synthesis *via* a palladium-catalyzed carboamination reaction.[34] Generally the products were formed in good yields and a variety of aryl halides can be used to introduce structural diversity. The reaction proceeds through 4-5 synthetic steps which require the isolation of the intermediates. Farfán reported a multi-step route for the synthesis of *N*-alkyl-*N*′-arylpiperazines using ethyl oxalyl chloride and *o*-aminophenol as the starting materials, which are further treated with norephedrine and reduced with BH_3 to give *N*-alkyl-*N*′-arylpiperazines.[35] Although this transformation provided high yields and excellent diastereoselectivity, this route is limited to terminal olefins and uses costly reagents and catalyst systems. Watanabe and co-workers published a pioneering ruthenium-catalyzed reaction to convert 1,5-diols and primary amines into *N*-alkyl-*N*′-arylpiperazines.[36] As opposed to the carboamination approach, this process uses inexpensive and readily available alcohols and only a catalytic amount of ruthenium catalyst. In 2015, Xie and co-workers reported a novel method for the synthesis of *N*-alkyl-*N*′-alkenylpiperazines in a reaction involving DABCO, electron-deficient acetylenes, and aryl acids.[37] This *N*-alkenylation reaction utilized highly activated acetylenic esters as the alkenyl source which limits the reaction scope. The study indicates that catalytic *N*-arylation and alkenylation of DABCO with aryl and alkenyl halides or triflates is almost a more effective procedure with respect to reaction scope, time, cost, and yield than those methods previously reported. Moreover, the method offers an opportunity for the synthesis of a wide range of *N*-aryl and –heteroaryl piperazine-containing drugs in a single step from the readily available reactants without the isolation of the intermediates. While, the present method is limited to the production of piperazines which have substitutions on both nitrogen atoms and suffers from the low atom economy.

The reaction conducted with **5** (isolated salt) and **3a** in optimum reaction conditions described in Table 1, formed **4a** in 81% yield. It could be deduced that the reaction starts with the formation of **5**, followed by coordination of the ionic adduct to the copper slat to give **6**. It is interesting for us to note that no product arising from the ring opening of DABCO formed when DABCO®-CuCl complex (0.5 mmol) was warmed up to 110 ˚C in the presence of LiCl (0.5 mmol) in NMP.

Aryl triflate **3** could be oxidatively added to the Cu(I)-complex **6** to form a Cu(III)-intermediate **7**. Reductive elimination of intermediate **7** could produce the arylammonium species **8** and releases the Cu(I) species. The intermediate is further converted to **9** through the ring-opening prompted by nucleophilic attack of chloride ion, which finally give the desired aminated product **4** by reacting with *t*-BuOLi in a Hofmann type elimination reaction. The latter elimination is further supported by the fact that when the reaction was conducted with benzyl iodide instead of benzyl chloride, iodoethene is detected by crude GC-MS analysis. Note that no the desired product formation occurred when benzyl triflate was employed as the alkyl source. This result proposed that the reaction proceeds through the nucleophilic attack of halide ion on the corresponding bicyclic quaternary ammonium salt.

In conclusion, we have attempted to demonstrate the importance of the reaction parameters for enabling unique reactivity and selectivity in C-N bond formation. Methods for selective synthesis of *N*-alkyl-*N*′-aryl or alkenylpiperazines represent an important class of C–N bond formation, and the reactions described above highlight the utility of such methods in the synthesis of a wide range of piperazines-containing drugs. These reactions achieve good conversions and acceptable product yields, and the catalyst tolerates useful substrate functional groups. Further studies are being conducted to develop the reaction scope with poorer leaving groups like –OTs and–$OPO(OPh)_2$.

Experimental Part

Alkyl chlorides, DABCO, solvents, bases, and catalyst were obtained from Merck and were used without further purification. Aryl and alkenyl triflates were obtained from Hangzhou Yuhao Chemical Technology Co., Ltd. Melting points were measured with Electrothermal-9100 apparatus. IR Spectra were recorded with Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded with Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; in ppm. Mass spectra were recorded with EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Column chromatography was performed using silica gel 60 (particle size 63–200 μm) (Merck, item number 7734-3). TLC was performed using silica gel 60 (Merck, item number 116835). Known compounds (**4a**, **4c**, **4d**, and **4e**) gave satisfactory ^{1}H-NMR and ^{13}C-NMR data and were consistent with that reported in the literature.

Compounds **4**: *General Procedure.* A mixture of DABCO (1.2-1.5 mmol, see Table 2 and 3) and alkyl chloride (1.0 mmol) was stirred for 15 min in neat reaction condition. Then, aryl or alkenyl triflate (1.0 mmol), CuCl (0.05-0.1 mmol, see Table 2 and 3), *t*-BuOLi (1.5 mmol), and NMP (3 mL, see Table 2 and 3) were added and the mixture was stirred for 14-18 h at 70-90 °C. After completion of the reaction, it was diluted by EtOAc (5 mL) and a saturated NH_4Cl solution (5 mL). The mixture was stirred for additional 30 min and two layers were separated. The aqueous layer was then extracted with EtOAc (3 ×8 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexane:EtOAc 4:1) to give the desired product.

1-Benzyl-4-(2-naphthyl)piperazine (**4b**)

Pale yellow oil; yield: 0.26 g (85%). IR (KBr) (ν_{max}, cm^{-1}): 2961, 1631, 1511, 1328, 1189. ^{1}H NMR(500 MHz, $CDCl_3$): δ_H= 2.76 (4 H, t, ^{3}J = 6.9 Hz, 2 CH_2), 3.30 (4 H, t, ^{3}J = 6.9

Hz, 2 CH_2), 3.60 (2 H, s, CH_2N), 7.04 (1 H, s, CH), 7.20 (2 H, t, ^3J = 6.5 Hz, 2 CH), 7.33 (1 H, t, ^3J = 6.5 Hz, CH), 7.36 (1 H, d, ^3J = 6.6 Hz, CH), 7.41 (2 H, d, ^3J = 6.6 Hz, 2 CH), 7.45 (2 H, t, ^3J = 6.9 Hz, 2 CH), 7.71 (3 H, d, ^3J = 8.7 Hz, 3 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 49.0 (2 CH_2), 54.5 (2 CH_2), 61.9 (CH_2N), 108.1 (CH), 118.1 (CH), 124.3 (CH), 127.0 (CH), 128.1 (CH), 128.4 (CH), 129.0 (CH), 129.3 (2 CH), 129.4 (C), 129.6 (CH), 130.9 (2 CH), 134.6 (C), 137.9 (C), 149.2 (C). MS: *m/z* (%) = 302 (M^+, 1), 287 (15), 146 (24), 91 (100), 56 (45). Anal. Calcd for $C_{21}H_{22}N_2$ (302.42): C, 83.40; H, 7.33; N, 9.26%; Found: C, 83.60; H, 7.48; N, 9.48%.

1-benzyl-4-(4-(tert-butyl)phenyl)piperazine (**4f**)

Pale yellow oil; yield: 0.24 g (79%). IR (KBr) (ν_{max}, cm^{-1}): 2934, 1604, 1510, 1348, 1142. ^{1}H NMR(500 MHz, $CDCl_3$) δ_H = 1.46 (9 H, s, 3 Me), 2.71 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.34 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.76 (2 H, s, CH_2N), 6.71 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.01 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.27-7.36 (5 H, m, 5 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 33.2 (3 Me), 36.8 (C), 49.1 (2 CH_2), 54.8 (2 CH_2), 67.3 (CH_2N), 114.3 (2 CH), 128.3 (2 CH), 128.9 (CH), 129.3 (2 CH), 129.7 (2 CH), 137.1 (C), 141.3 (C), 148.9 (C). MS: *m/z* (%) = 308 (M^+, 3), 251 (45), 133 (34), 91 (100), 77 (26), 57 (83). Anal. Calcd for $C_{21}H_{28}N_2$ (308.47): C, 81.77; H, 9.15; N, 9.08%; Found C, 82.04; H, 9.42; N, 9.15%.

1-(4-(4-benzylpiperazin-1-yl)phenyl)ethan-1-one (**4g**).

Pale yellow oil; yield: 0.27 g (91%). IR (KBr) (ν_{max}, cm^{-1}): 2932, 2832, 1718, 1579, 1464, 1248. ^{1}H NMR(500 MHz, $CDCl_3$): δ_H = 2.58 (3 H, s, Me), 2.69 (4 H, t, ^3J = 5.5 Hz, 2 CH_2), 3.29 (4 H, t, ^3J = 5.5 Hz, 2 CH_2), 3.79 (2 H, s, CH_2N), 7.03 (2 H, d, ^3J = 7.2 Hz, 2 CH), 7.26-7.34 (5 H, m, 5 CH), 7.86 (2 H, t, ^3J = 7.2 Hz, 2 CH). ^{13}C NMR (125.7 MHz,

$CDCl_3$): δ_C = 28.1 (Me), 51.0 (2 CH_2), 59.7 (2 CH_2), 67.9 (CH_2N), 126.4 (2 CH), 127.6 (CH), 128.9 (2 CH), 129.2 (2 CH), 130.3 (2 CH), 132.3 (C), 136.8 (C), 139.2 (C), 198.5 (C). MS: *m/z* (%) = 294 (M^+, 11), 175 (31), 119 (56), 91 (100), 56 (16). Anal. Calcd for $C_{19}H_{22}N_2O$ (294.40): C, 77.52; H, 7.53; N, 9.52%; Found: C, 77.91; H, 7.68; N, 9.47%..

4-(4-butylpiperazin-1-yl)benzonitrile (**4h**)

Colorless solid, mp: 108-111 ˚C; Yield: 0.21 g (88%). IR (KBr) (ν_{max}, cm^{-1}): 2944, 2236, 1603, 1496, 1217. ^{1}H NMR(500 MHz, $CDCl_3$): δ_H = 0.97 (3 H, t, ^3J = 7.3 Hz, CH_3), 1.30-1.44 (4 H, m, 2 CH_2), 2.79 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.17 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.35 (2 H, t, ^3J = 7.5 Hz, CH_2N), 6.98 (2 H, d, ^3J = 8.3 Hz, 2 CH), 7.41 (2 H, d, ^3J = 8.3 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 15.3 (CH_3), 23.4 (CH_2), 29.8 (CH_2), 50.1 (2 CH_2), 55.2 (2 CH_2), 57.1 (CH_2N), 105.5 (C), 116.3 (2 CH), 117.1 (CN), 132.8 (2 CH), 154.3 (C). MS: *m/z* (%) = 243 (M^+, 75), 217 (100), 141 (56), 102 (15), 77 (22), 57 (11). Anal.Calcd for $C_{15}H_{21}N_3$ (243.35): C, 74.03; H, 8.70; N, 17.27%; Found: C, 74.39; H, 8.98; N, 17.11%.

1-butyl-4-(pyridin-2-yl)piperazine (**4i**)

Yellow oil; yield: 0.20 g (91%). IR (KBr) (ν_{max}, cm^{-1}): 3041, 2969, 16280, 1325, 1110. ^{1}H NMR(500 MHz, $CDCl_3$): δ_H = 0.91 (3 H, t, ^3J = 7.3 Hz, CH_3), 1.32-1.47 (4 H, m, 2 CH_2), 2.83 (4 H, t, ^3J = 5.2 Hz, 2 CH_2), 3.36 (4 H, t, ^3J = 5.2 Hz, 2 CH_2), 3.79 (2 H, t, ^3J = 7.1 Hz, CH_2N), 6.76-6.81 (2 H, m, 2 CH), 7.67 (1 H, t, ^3J = 7.9 Hz, CH), 8.13 (1 H, t, ^3J = 7.3 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 24.1 (CH_2), 29.2 (CH_2), 48.6 (2 CH_2), 52.3 (2 CH_2), 55.5 (CH_2N), 107.3 (CH), 118.2 (CH), 139.1 (CH), 149.2 (CH), 162.3 (C). MS: *m/z*(%) = 219 (M^+, 15), 162 (13), 141 (54), 85 (34), 78 (100), 58 (13). Anal.

Calcd for $C_{13}H_{21}N_3$ (219.33): C, 71.19; H, 9.65; N, 19.16%; Found C, 71.35; H, 9.98; N, 19.13%.

6-(4-butylpiperazin-1-yl)quinoline (**4j**)

Yellow oil; yield: 0.23 g (84%). IR (KBr) (ν_{max}, cm^{-1}): 2961, 1631, 1511, 1328, 1189. ^1H NMR(500 MHz, $CDCl_3$): δ_H= 0.96 (3 H, t, ^3J = 7.3 Hz, CH_3), 1.34-1.45 (4 H, m, 2 CH_2), 2.88 (4 H, t, ^3J = 5.3 Hz, 2 CH_2), 3.25 (4 H, t, ^3J = 5.3 Hz, 2 CH_2), 3.46 (2 H, t, ^3J = 7.1 Hz, CH_2N), 6.79 (1 H, s, CH), 7.28 (1 H, t, ^3J = 6.5 Hz, CH), 7.65 (1 H, d, ^3J = 6.8 Hz, CH), 8.36-846 (2 H, m, 2 CH), 8.78 (1 H, d, ^3J = 6.6 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 15.1 (CH_3), 22.1 (CH_2), 31.3 (CH_2), 51.6 (2 CH_2), 54.5 (2 CH_2), 57.1 (CH_2N), 121.1 (CH), 122.2 (CH), 124.3 (CH), 128.2 (CH), 133.1 (C), 136.1 (CH), 143.7 (C), 147.9 (2 CH), 151.4 (C). MS: *m/z* (%) = 269 (M^+, 13), 212 (18), 141 (22), 128 (100), 56 (38). Anal. Calcd for $C_{17}H_{23}N_3$ (269.39): C, 75.80; H, 8.61; N, 15.60%; Found: C, 75.97; H, 8.79; N, 15.73%.

1-benzyl-4-(4-nitrophenyl)piperazine (**4k**)

Yellow solid, mp: 151-153 ˚C; yield: 0.28 g (93%). IR (KBr) (ν_{max}, cm^{-1}): 2944, 1595, 1536, 1351, 1237. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.68 (4 H, t, ^3J = 5.5 Hz, 2 CH_2), 3.45 (4 H, t, ^3J = 5.5 Hz, 2 CH_2), 3.78 (2 H, s, CH_2N), 7.11 (2 H, t, ^3J = 7.3 Hz, 2 CH), 7.27-7.34 (5 H, m, 5 CH), 8.21 (2 H, t, ^3J = 7.3 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 54.9 (2 CH_2), 59.3 (2 CH_2), 65.1 (CH_2N), 115.1 (2 CH), 126.3 (2 CH), 127.1 (CH), 129.1 (2 CH), 129.8 (2 CH), 136.1 (C), 139.2 (C), 157.3 (C). MS: *m/z* (%) = 297 (M^+, 13), 119 (58), 104 (35), 91 (100), 77 (27), 56 (66). Anal. Calcd for $C_{17}H_{19}N_3O_2$ (297.36): C, 68.67; H, 6.44; N, 14.13%; Found: C, C, 68.93; H, 6.56; N, 14.24%.

1-butyl-4-(4-nitrophenyl)piperazine (**4l**)

Yellow solid, mp: 98-101 ˚C; yield: 0.24 g (91%). IR (KBr) (ν_{max}, cm^{-1}): 3041, 2965, 1539, 1368, 1207. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.87 (3 H, t, ^3J = 7.0 Hz, CH_3), 1.33-1.45 (4 H, m, 2 CH_2), 2.83 (2 H, t, ^3J = 6.8 Hz, CH_2N), 3.11 (4 H, t, ^3J = 5.9 Hz, CH_2), 3.52 (4 H, t, ^3J = 5.9 Hz, 2 CH_2), 7.13 (2 H, t, ^3J = 6.7 Hz, 2 CH), 8.16 (2 H, t, ^3J = 6.7 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 14.1 (CH_3), 26.2 (CH_2), 31.3 (CH_2), 51.7 (2 CH_2), 56.1 (CH_2N), 59.3 (2 CH_2), 116.3 (2 CH), 127.5 (2 CH), 138.5 (C), 156.9 (C). MS: *m/z* (%) = 263 (M^+, 8), 206 (21), 141 (35), 122 (100), 77 (16), 56 (67). Anal. Calcd for $C_{14}H_{21}N_3O_2$ (263.34): C, 63.85; H, 8.04; N, 15.96%; Found: C, C, 64.23; H, 8.36; N, 15.87%.

1-hexyl-4-(4-nitrophenyl)piperazine (**4m**)

Yellow solid, mp: 105-108 ˚C; yield: 0.27 g (93%). IR (KBr) (ν_{max}, cm^{-1}): 3047, 2948, 1553, 1348, 1235. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.91 (3 H, t, ^3J = 6.7 Hz, CH_3), 1.30-1.49 (8 H, m, 4 CH_2), 2.78 (2 H, t, ^3J = 6.3 Hz, CH_2N), 3.11 (4 H, t, ^3J = 6.8 Hz, CH_2), 3.49 (4 H, t, ^3J = 5.0 Hz, 2 CH_2), 7.11 (2 H, d, ^3J = 7.0 Hz, 2 CH), 8.13 (2 H, t, ^3J = 7.0 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.1 (CH_3), 21.5 (CH_2), 27.8 (CH_2), 28.3 (CH_2), 32.5 (CH_2), 50.3 (2 CH_2), 51.4 (CH_2N), 57.2 (2 CH_2), 115.8 (2 CH), 126.3 (2 CH), 138.1 (C), 156.5 (C). MS: *m/z* (%) = 291 (M^+, 36), 206 (27), 169 (100), 122 (34), 56 (13). Anal.Calcd for $C_{16}H_{25}N_3O_2$ (291.40): C, 65.95; H, 8.65; N, 14.42%; Found: C, 66.23; H, 8.97; N, 14.58%

1-benzyl-4-(4-(tert-butyl)cyclohex-1-en-1-yl)piperazine (**4n**)

Pale yellow oil, yield: 0.25 g (80%).IR (KBr) (ν_{max}, cm^{-1}): 2937, 1600, 1501, 1237. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.93 (9 H, s, 3 CH_3), 1.39-2.27 (9 H, m, 9 CH), 2.78 (4 H, t, ^3J = 5.3 Hz, 2 CH_2), 3.13 (4 H, t, ^3J = 5.3 Hz, 2 CH_2), 3.67 (2 H, s, CH_2N), 4.58 (1 H, t, ^3J = 6.2 Hz, CH), 7.23-7.29 (5 H, m, 5 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 22.3 (CH_2), 24.1 (CH_2), 25.8 (CH_2), 29.3 (3 CH_3), 34.9 (C), 47.1 (CH), 49.9 (2 CH_2), 54.8 (2 CH_2), 64.2 (CH_2N), 101.3 (CH), 127.6 (2 CH), 127.9 (CH), 129.1 (2 CH), 137.2 (C), 146.9 (C). MS: *m/z* (%) = 312 (M^+, 23), 225 (13), 137 (59), 91 (100), 77 (56), 57 (89). Anal. Calcd for $C_{21}H_{32}N_2$ (312.50): C, 80.71; H, 10.32; N, 8.96%; Found: C, 80.98; H, 10.67; N, 9.13%.

1-benzyl-4-(3-phenylprop-1-en-1-yl)piperazine (**4o**).

Pale yellow oil; yield: 0.25 g (86%). IR (KBr) (ν_{max}, cm^{-1}): 3049, 2941, 1655, 1581, 1237. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.69 (4 H, t, ^3J = 6.2 Hz, 2 CH_2), 3.28 (2 H, s, CH_2), 3.45 (4 H, t, ^3J = 6.2 Hz, 2 CH_2), 3.68 (2 H, s, CH_2N), 5.11 (1 H, m, CH), 5.87 (1 H, d, ^3J = 11.8 Hz, CH), 7.20-7.31 (10 H, m, 10 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 37.1 (CH_2), 49.1 (2 CH_2), 55.6 (2 CH_2), 66.3 (CH_2N), 104.5 (CH), 126.1 (CH), 126.5 (CH), 127.4 (2 CH), 128.4 (2 CH), 129.3 (2 CH), 129.9 (2 CH), 137.8 (C), 139.2 (CH), 141.0 (C). MS: *m/z* (%) = 292 (M^+, 11), 201 (13), 175 (35), 117 (39), 91 (100), 77 (61). Anal. Calcd for $C_{20}H_{24}N_2$ (292.43): C, 82.15; H, 8.27; N, 9.58%; Found: C, C, 82.43; H, 8.51; N, 9.70%.

1-benzyl-4-(2-cyclohexylvinyl)piperazine (**4p**).

Pale yellow oil; yield: 0.22 g (78%). IR (KBr) (ν_{max}, cm^{-1}): 2961, 1585, 1511, 1226. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 1.32-1.68 (10 H, m, 10 CH), 2.57 (1 H, m, CH), 2.79 (4 H, t, ^3J = 5.7 Hz, 2 CH_2), 3.41 (4 H, t, ^3J = 5.7 Hz, 2 CH_2), 3.76 (2 H, s, CH_2N), 4.81 (1 H, dd, ^3J = 11.1 Hz, CH), 5.88 (1 H, d, ^3J = 11.1 Hz, CH), 7.23-7.28 (5 H, m, 5 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 27.1 (2 CH_2), 28.3 (CH_2), 36.4 (2 CH_2), 38.2 (CH), 51.4 (2 CH_2), 57.2 (2 CH_2), 65.3 (CH_2N), 105.2 (CH), 127.2 (CH), 128.3 (2 CH), 128.9 (2 CH), 138.1 (C), 142.5 (C). MS: *m/z* (%) = 284 (M^+, 15), 175 (18), 109 (68), 91 (100), 83 (79), 77 (46), 56 (42). Anal. Calcd for $C_{19}H_{28}N_2$ (284.45): C, 80.23; H, 9.92; N, 9.85%; Found: C, 80.46; H, 10.19; N, 9.79%.

1-benzyl-4-(1-phenylvinyl)piperazine (**4q**).

Pale yellow oil; yield: 0.25 g (89%). IR (KBr) (ν_{max}, cm^{-1}): 3027, 2940, 1631, 1509, 1221. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 2.61 (4 H, t, ^3J = 5.9 Hz, 2 CH_2), 3.48 (4 H, t, ^3J = 5.9 Hz, 2 CH_2), 3.62 (2 H, s, CH_2N), 4.11 (1 H, d, ^2J = 3.9 Hz, CH), 4.53 (1 H, d, ^2J = 3.9 Hz, CH), 7.24-7.30 (5 H, m, 5 CH), 7.67-7.71 (3 H, m, 3 CH), 7.79 (2 H, d, ^3J = 7.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 51.8 (2 CH_2), 57.1 (2 CH_2), 65.8 (CH_2N), 103.1 (CH_2), 126.4 (CH), 127.2 (CH), 127.9 (2 CH), 128.5 (2 CH), 128.9 (2 CH), 129.7 (2 CH), 136.1 (C), 139.2 (C), 161.2 (C). MS: *m/z* (%) = 278 (M^+, 15), 187 (58), 175 (27), 103 (16), 91 (100), 77 (63), 56 (49). Anal. Calcd for $C_{19}H_{22}N_2$ (278.40): C, 81.97; H, 7.97; N, 10.06%; Found C, 82.24; H, 8.32; N, 10.15%.

1-benzyl-4-(non-1-en-1-yl)piperazine (**4r**)

Pale yellow oil; yield: 0.25 g (83%). IR (KBr) (ν_{max}, cm^{-1}): 3018, 2972, 1610, 1519, 1217. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.91 (3 H, t, ^3J = 6.7 Hz, CH_3), 1.28-1.37 (10 H, m, 5 CH_2), 2.28-2.32 (2 H, m, CH_2), 2.69 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.41 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.55 (2 H, s, CH_2N), 4.61-4.65 (1 H, m, CH), 5.91 (1 H, d, ^3J = 10.9 Hz, CH), 7.24-7.30 (5 H, m, 5 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 14.6 (CH_3), 25.1 (CH_2), 26.3 (CH_2), 28.2 (CH_2), 29.5 (CH_2), 29.9 (CH_2), 33.1 (CH_2), 48.9 (2 CH_2), 571 (2 CH_2), 67.1 (CH_2N), 106.4 (CH), 125.6 (CH), 127.6 (2 CH), 128.9 (2 CH), 136.1 (C), 139.8 (C). MS: *m/z* (%) = 300 (M^+, 15), 175 (29), 125 (11), 91 (100), 77 (69), 56 (48). Anal. Calcd for $C_{20}H_{32}N_3$ (300.49): C, 79.94; H, 10.73; N, 9.32%; Found: C, 80.26; H, 10.98; N, 9.28%.

1-benzyl-4-(3-styrylcyclopent-1-en-1-yl)piperazine (**4s**)

Pale yellow oil; yield: 0.33 g (88%). IR (KBr) (ν_{max}, cm^{-1}): 3047, 2975, 1648, 1530, 1216. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 1.87-2.28 (4 H, m, 4 CH), 2.61 (4 H, t, ^3J = 6.4 Hz, 2 CH_2), 3.51 (4 H, t, ^3J = 6.4 Hz, 2 CH_2), 3.58 (1 H, t, ^3J = 7.1 Hz, CH), 3.67 (2 H, s, CH_2N), 4.61 (1 H, d, ^3J = 7.1 Hz, CH), 6.11 (1 H, m, CH), 6.49 (1 H, d, ^3J = 6.7 Hz, CH), 7.25-7.36 (6 H, m, 6 CH), 7.41 (2 H, t, ^3J = 6.9 Hz, 2 CH), 7.64 (2 H, d, ^3J = 6.9 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 28.1 (CH_2), 35.1 (CH_2), 38.3 (CH), 49.9 (2 CH_2), 53.7 (2 CH_2), 65.4 (CH_2N), 100.1 (CH), 117.9 (CH), 125.2 (CH), 126.2 (CH), 127.6 (2 CH), 128.1 (2 CH), 128.6 (CH), 129.6 (2 CH), 131.3 (CH), 135.5 (C), 139.2 (C), 153.1 (C). MS: *m/z* (%) = 344 (M^+, 11), 241 (13), 175 (35), 169 (26), 91 (100), 77 (68). Anal. Calcd for $C_{24}H_{28}N_2$ (344.50): C, 83.68; H, 8.19; N, 8.13%; Found: C, 83.91; H, 8.27; N, 8.31%.

1-benzyl-4-(non-4-en-4-yl)piperazine (**4t**)

Pale yellow oil; yield: 0.23 g (78%). IR (KBr) (ν_{max}, cm^{-1}): 3023, 2965, 1658, 1519, 1237. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.91-0.95 (6 H, m, 2 CH_3), 1.30-1.37 (6 H, m, 3 CH_2), 2.24-2.32 (4 H, m, 2 CH_2), 2.51 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.41 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.67 (2 H, s, CH_2), 4.48 (1 H, t, ^3J = 6.8 Hz, CH), 7.23-7.30 (5 H, m, 5 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 14.1 (CH_3), 23.9 (CH_2), 26.1 (CH_2), 27.8 (CH_2), 33.1 (CH_2), 35.9 (CH_2), 51.3 (2 CH_2), 57.8 (2 CH_2), 65.1 (CH_2N), 103.0 (CH), 126.1 (CH), 127.1 (2 CH), 129.2 (2 CH), 139.2 (C), 155.1 (C). MS: *m/z* (%) = 300 (M^+, 11), 209 (41), 175 (39), 125 (18), 91 (100), 77 (58). Anal.Calcd for $C_{20}H_{32}N_2$ (300.49): C, 79.94; H, 10.73; N, 9.32%; Found: C, 80.34; H, 10.96; N, 9.48%.

1-butyl-4-(1-phenylvinyl)piperazine (**4u**)

Colorless oil; yield: 0.19 g (78%). IR (KBr) (ν_{max}, cm^{-1}): 3061, 2967, 1645, 1321, 1267. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.82 (3 H, t, ^3J = 6.4 Hz, CH_3), 1.37-1.49 (4 H, m, 2 CH_2), 2.71 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.12 (2 H, t, ^3J = 5.9 Hz, CH_2N), 3.64 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.81 (1 H, d, ^2J = 4.2 Hz, CH), 4.73 (1 H, d, ^2J = 4.2 Hz, CH), 7.42 (2 H, t, ^3J = 6.2 Hz, 2 CH), 7.58 (1 H, t, ^3J = 6.2 Hz, 2 CH), 7.84 (2 H, d, ^3J = 6.7 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 15.1 (CH_3), 25.2 (CH_2), 35.1 (CH_2), 51.4 (2 CH_2), 59.1 (2 CH_2), 60.2 (CH_2N), 106.3 (CH_2), 126.7 (CH), 127.5 (2 CH), 128.2 (2 CH), 136.4 (C), 163.2 (C). MS: *m/z* (%) = 244 (M^+, 8), 187 (31), 141 (15), 112 (40), 102 (67), 77 (100), 57 (48). Anal. Calcd for $C_{19}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.46%; Found C, 78.87; H, 10.12; N, 11.61%.

1-hexyl-4-(1-phenylvinyl)piperazine (**4v**)

Colorless oil; yield: 0.21 g (76%). IR (KBr) (ν_{max}, cm^{-1}): 3058, 2978, 1647, 1541, 1342, 1226. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.83 (3 H, t, ^3J = 6.2 Hz, CH_3), 1.36-1.56 (8 H, m, 4 CH_2), 2.70 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.25 (2 H, t, ^3J = 5.6 Hz, CH_2), 3.67 (4 H, t, ^3J = 6.1 Hz, 2 CH_2), 3.87 (1 H, d, ^2J = 4.0 Hz, CH), 4.68 (1 H, d, ^2J = 4.0 Hz, CH), 7.38 (2 H, t, ^3J = 6.4 Hz, 2 CH), 7.65 (1 H, t, ^3J = 6.4 Hz, 2 CH), 7.81 (2 H, d, ^3J = 6.4 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 25.9 (CH_2), 32.3 (CH_2), 36.1 (CH_2), 38.5 (CH_2), 52.2 (2 CH_2), 57.9 (2 CH_2), 63.1 (CH_2N), 106.3 (CH_2), 126.9 (CH), 127.8 (2 CH), 128.9 (2 CH), 136.7 (C), 161.9 (C). MS: *m/z* (%) = 272 (M^+, 18), 187 (36), 169 (22), 112 (68), 85 (41), 77 (100), 56 (48). Anal. Calcd for $C_{18}H_{28}N_2$ (272.44): C, 79.36; H, 10.36; N, 10.28%; Found C, 79.58; H, 10.58; N, 10.39%.

1-allyl-4-(1-phenylvinyl)piperazine (**4w**)

Colorless oil; yield: 0.19 g (84%). IR (KBr) (ν_{max}, cm^{-1}): 3089, 2971, 1656, 1637, 1543, 1328, 1241. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 2.69 (4 H, t, ^3J = 5.6 Hz, 2 CH_2), 3.18 (2 H, td, ^3J = 5.8 Hz, ^3J = 1.8 Hz, CH_2N), 3.62 (4 H, t, ^3J = 5.6 Hz, 2 CH_2), 4.15 (1 H, d, ^2J = 3.9 Hz, CH), 4.67 (1 H, d, ^2J = 3.9 Hz, CH), 5.24-5.26 (2 H, m, 2 CH), 6.04 (1 H, m, CH), 7.44-7.51 (3 H, m, 3 CH), 7.82 (2 H, d, ^3J = 6.4 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 50.2 (2 CH_2), 60.2 (2 CH_2), 62.1 (CH_2N), 105.5 (CH_2), 119.1 (CH_2), 126.8 (CH), 128.4 (2 CH), 128.9 (2 CH), 135.8 (CH), 137.1 (C), 160.6 (C). MS: *m/z* (%) = 228 (M^+, 3), 187 (39), 124 (43), 102 (68), 77 (100), 56 (48), 41 (61). Anal. Calcd for $C_{15}H_{20}N_2$ (228.34): C, 78.90; H, 8.83; N, 12.27%; Found C, 79.14; H, 8.97; N, 12.46%.

1-isobutyl-4-(1-phenylvinyl)piperazine (**4x**)

Colorless oil; yield: 0.15 g (61%). IR (KBr) (ν_{max}, cm^{-1}): 3037, 2968, 1651, 1327, 1251. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 0.96 (6 H, d, ^3J = 5.5 Hz, 2 CH_3), 1.89 (1 H, m, CH), 2.48 (2 H, s, CH_2N), 2.73 (4 H, t, ^3J = 5.7 Hz, 2 CH_2), 3.61 (4 H, t, ^3J = 5.7 Hz, 2 CH_2), 4.16 (1 H, d, ^2J = 3.6 Hz, CH), 4.68 (1 H, d, ^2J = 3.6 Hz, CH), 7.48-7.55 (3 H, m, 3 CH), 7.81 (2 H, d, ^3J = 6.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.1 (2 CH_3), 30.1 (CH), 53.1 (2 CH_2), 60.5 (2 CH_2), 73.1 (CH_2N), 106.9 (CH_2), 126.1 (CH), 127.9 (2 CH), 128.5 (2 CH), 136.5 (C), 161.0 (C). MS: *m/z* (%) = 244 (M^+, 4), 187 (41), 141 (30), 112 (58), 102 (79), 77 (100), 57 (83). Anal. Calcd for $C_{16}H_{24}N_2$ (244.38): C, 78.64; H, 9.90; N, 11.46%; Found C, 78.89; H, 10.24; N, 11.72%.

1-isopropyl-4-(1-phenylvinyl)piperazine (**4y**)

Colorless oil; yield: 0.11 g (46%). IR (KBr) (ν_{max}, cm^{-1}): 3045, 2961, 1646, 1521, 1341, 1221. ^1H NMR(500 MHz, $CDCl_3$): δ_H = 1.13 (6 H, d, ^3J = 5.2 Hz, 2 CH_3), 2.68 (4 H, t, ^3J = 5.9 Hz, 2 CH_2), 3.11 (1 H, q, ^3J = 5.2 Hz, CH_2N), 3.51 (4 H, t, ^3J = 5.9 Hz, 2 CH_2), 4.11 (1 H, d, ^2J = 3.9 Hz, CH), 4.71 (1 H, d, ^2J = 3.9 Hz, CH), 7.51 (1 H, t, ^3J = 6.1 Hz, CH), 7.60 (2 H, t, ^3J = 6.5 Hz, 2 CH), 7.85 (2 H, d, ^3J = 6.7 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.8 (2 CH_3), 54.8 (2 CH_2), 57.1 (2 CH_2), 69.4 (CHN), 105.1 (CH_2), 126.5 (CH), 128.2 (2 CH), 128.9 (2 CH), 136.1 (C), 160.3 (C). MS: *m/z* (%) = 230 (M^+, 2), 187 (42), 152 (36), 102 (67), 77 (100), 56 (49). Anal. Calcd for $C_{15}H_{22}N_2$ (230.36): C, 78.21; H, 9.63; N, 12.16%; Found C, 78.47; H, 9.85; N, 12.23%.

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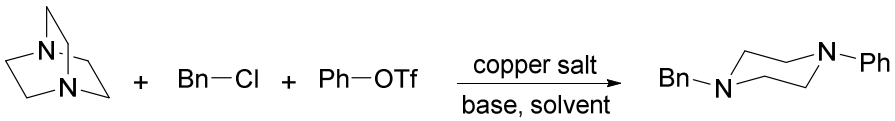
Table 1. Optimization of reaction conditions[a]



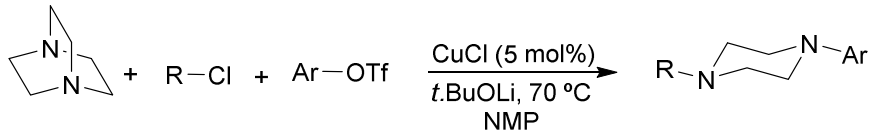
1 **2a** **3a** **4a**

Entry	Catalyst	Solvent	Base	Yield (%)
1	Cu(OTf)	NMP	*t*-BuOLi	86
2	CuCl	NMP	*t*-BuOLi	80
3	CuBr	NMP	*t*-BuOLi	traces
4	$CuBr.Me_2S$	NMP	*t*-BuOLi	35
5	CuI	NMP	*t*-BuOLi	29
6	Cu_2O	NMP	*t*-BuOLi	48
7	CuF_2	NMP	*t*-BuOLi	16
8	$CuBr_2$	NMP	*t*-BuOLi	traces
9	$Cu(BF_4)_2$	NMP	*t*-BuOLi	traces
10	CuCl	NMP	*t*-BuOCs	traces
11	CuCl	NMP	*t*-BuOK	21
12	CuCl	NMP	Li_2CO_3	-
13	CuCl	NMP	K_3PO_4	-
14	CuCl	NMP	EtOLi	-
15	CuCl	DMF	*t*-BuOLi	23
16	CuCl	DMSO	*t*-BuOLi	29
17	CuCl	DMA	*t*-BuOLi	53
18	CuCl	HMPA	*t*-BuOLi	traces
19	CuCl	toluene	*t*-BuOLi	16
20	CuCl	dioxane	*t*-BuOLi	-
21	CuCl	Ethylene glycol	*t*-BuOLi	29
22	CuCl	NMP	*t*-BuOK	78[b]

[a] Reaction conditions: DABCO (1.2 mmol), benzyl chloride (1.0 mmol), phenyl trifluoromethanesulfonate (1.0 mmol), base (1.5 mmol), copper salt (0.05 mmol), solvent (3 mL), 70 ˚C, 14 h.

[b] Reaction mixture was stirred at 110 ˚C.

Table 2. Synthesis of unsymmetrical piperazines using aryl triflates[a]



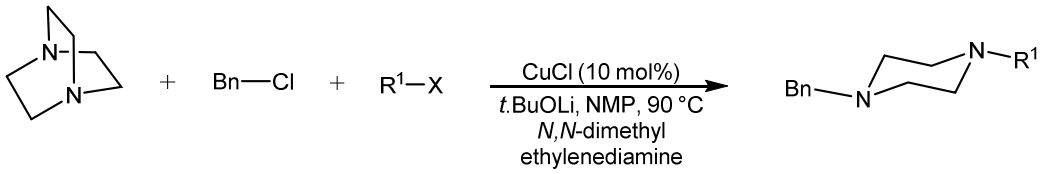
1 **2** **3** **4**

Entry	**2**	R	**3**	Ar	Product	Yield (%)
1	**2a**	Bn	**3a**	Ph	**4a**	86
2	**2a**	Bn	**3b**	2-naphthyl	**4b**	85
3	**2a**	Bn	**3c**	4-MeC_6H_4	**4c**	80[b]
4	**2a**	Bn	**3d**	3-MeC_6H_4	**4d**	82[b]
5	**2a**	Bn	**3e**	3-$MeOC_6H_4$	**4e**	73[b]
6	**2a**	Bn	**3f**	4-*t*.BuC_6H_4	**4f**	79[b]
7	**2a**	Bn	**3g**	4-Acetylphenyl	**4g**	91
8	**2a**	Bu	**3h**	4-CNC_6H_4	**4h**	88
9	**2a**	Bu	**3i**	2-Pyridyl	**4i**	91
10	**2a**	Bu	**3j**	6-quinolyl	**4j**	84
11	**2a**	Bn	**3k**	4-$NO_2C_6H_4$	**4k**	93
12	**2b**	*n*-Bu	**3k**	4-$NO_2C_6H_4$	**4l**	91
13	**2c**	*n*-Hexyl	**3k**	4-$NO_2C_6H_4$	**4m**	93

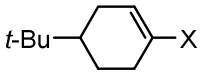
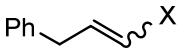
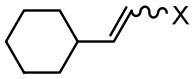
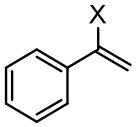
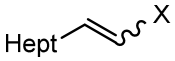
[a]For all entries except stated otherwise: **1** (1.2 mmol), **2** (1.0 mmol), **3** (1.0 mmol), *t*-BuOLi (1.5 mmol), CuCl (0.05 mmol), NMP (3.0 mL), 70 ˚C, 14 h.

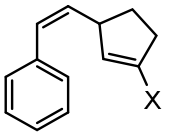
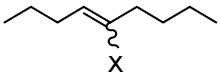
[b]Reactions were conducted with 1.5 mmol of **1** using 0.1 mmol of CuCl.

Table 3. Synthesis of unsymmetrical piperazines using alkenyl iodide and triflate[a]



1 **2a** **5** **4**

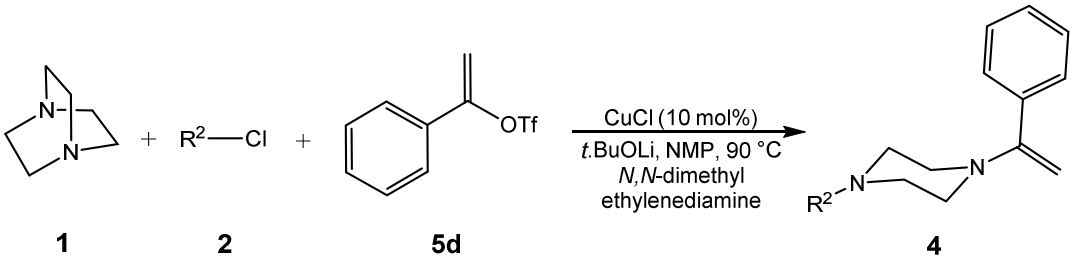
Entry	**5**	Product	Yield (%) X = I	Yield (%) X = OTf
1	 **5a**	**4n**	80	73
2	 (7/93)[b] **5b**	**4o**	86	71(3/97)[b]
3	 (95/5)[b] **5c**	**4p**	78	65(99/1)[b]
4	 **5d**	**4q**	89	85
5	 (92/8)[b]	**4r**	83	69(96/4)[b]

	5e			
6		**4s**	88	73
	5f			
7		**4t**	78	63
	5g			

[a]For all entries: **1** (1.2 mmol), **2a** (1.0 mmol), **5** (1.0 mmol), *t*-BuOLi (1.5 mmol), CuCl (0.10 mmol), *N*, *N*′-dimethyl ethylenediamine (0.10 mmol), NMP (3.0 mL), 90 ˚C, 18 h.

[b]The digit in parentheses described the E/Z ratio.

Table 4. Synthesis of unsymmetrical piperazines using different alkyl chloride and **5d**[a]

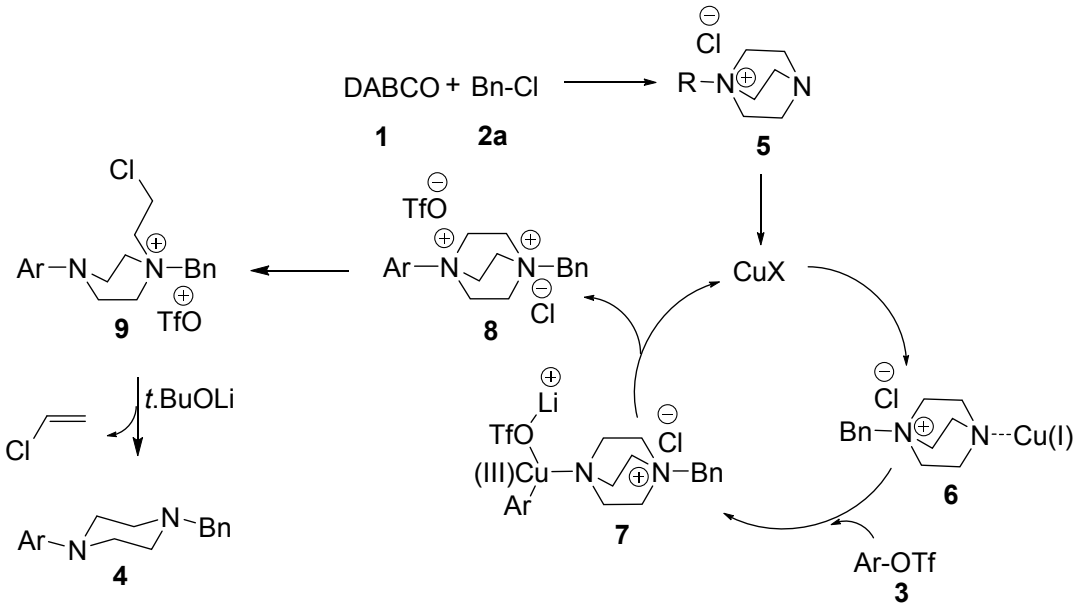


1 **2** **5d** **4**

Entry	2	R^2	Product	Yield (%)
1	**2b**	*n*-Bu	**4u**	78
2	**2c**	*n*-Hexyl	**4v**	76
3	**2d**	Allyl	**4w**	84
4	**2e**	2-Methylpropane	**4x**	61
5	**2f**	*i*.Pr	**4y**	46

[a]For all entries: **1** (1.2 mmol), **2** (1.0 mmol), **5d** (1.0 mmol), *t*-BuOLi (1.5 mmol), CuCl (0.10 mmol), *N, N*′-dimethyl ethylenediamine (0.10 mmol), NMP (3.0 mL), 90 ˚C, 22 h.

Scheme 1



Scheme 1. Proposed mechanism for the formation of unsymmetrical piperazines