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Dicationic Ring-Opening Reactions of *trans*-2-Phenylcyclopropylamine·HCl: Electrophilic Cleavage of the Distal (C_2−C_3) Bond of Cyclopropanes

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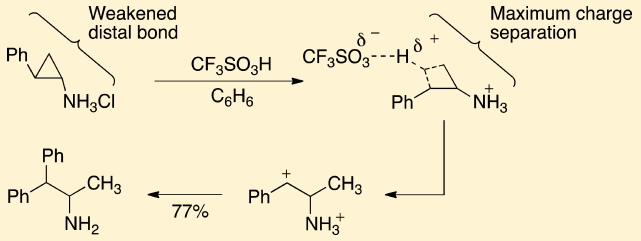
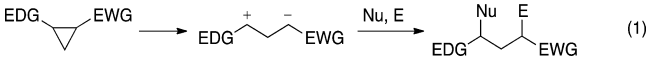
Supporting Information

ABSTRACT: Electrophilic ring opening of *trans*-2-phenylcyclopropylamine·HCl occurs at the distal (C_2−C_3) bond. This is consistent with weakening of the distal bond by the σ-withdrawing ammonium group and charge−charge repulsive effects in the transition state.



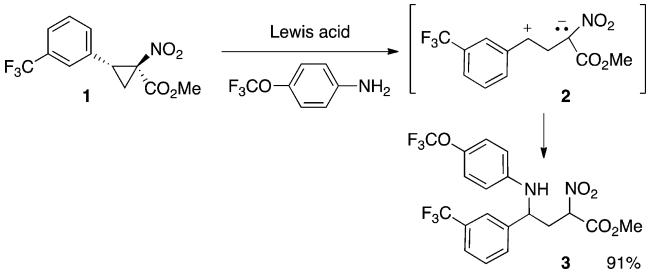
Cyclopropane ring-opening reactions have been the subject of a vast number of synthetic, mechanistic, and biological studies.[1] Among the synthetic reactions, the ring-opening reactions of donor−acceptor cyclopropanes have been particularly useful.[2−7] With ring opening by bond heterolysis, the vicinal bond generally undergoes cleavage to form the zwitterionic species wherein the charge centers are stabilized by the appropriate substitutents (eq 1).[8] This is often followed by



(1)

reactions with a nucleophile and an electrophile. Among recent examples of this chemistry, Mattson and co-workers used a boronate urea Lewis acid to promote ring opening of nitrocyclopropane **1** (Scheme 1).[9] Reaction of the zwitterionic species **2** with 4-(trifluoromethoxy)aniline provides the addition product **3** in good yield. Further synthetic steps provide a CB-1 receptor inverse agonist drug from intermediate **3**.

Scheme 1. Donor−Acceptor Ring Opening of Cyclopropane 1



It has long been thought that donor−acceptor cyclopropane ring-opening reactions involve electron donation into the π-acceptor groups. Theoretical studies by Cruz-Cabeza and Allen and by Clark and Schleyer have suggested that these processes involve interaction of the 3e′ orbital of the cyclopropane ring with the low-lying unoccupied orbital of the π-acceptor substituent group(s).[10] This interaction leads to weakening and lengthening of the vicinal (C_1−C_2) bond of the cyclopropane and can lead to bond heterolysis. Interestingly, strong σ-acceptor groups are predicted to interact with the cyclopropane 1e″ orbital, leading to lengthening (and weakening) of the distal (C_2−C_3) bond of the cyclopropane. This theoretical prediction has been confirmed by crystallographic data from cyclopropanes having strong σ-acceptor groups. For example, 1,1-difluorocyclopropane has vicinal and distal C−C bond lengths of 1.468 and 1.540 Å, respectively.[11] The lengthened and weakened distal bond of 1,1-difluorocyclopropane is well-known for its tendency to undergo bond homolysis reactions.[12] In this note, we describe the ring-opening reactions of *trans*-2-phenylcyclopropylamine·HCl in superacid and trapping of the resulting ammonium−carbenium dication with arene nucleophiles. This chemistry is a rare example of distal bond cleavage accompanied by nucleophilic and electrophilic reactions. The observed chemical reactions are in accord with the theoretical predictions made by Clark and Schleyer.[10a]

Our studies began with the superacidic reaction of cyclopropane **4** (tranylcypromine, a clinically useful antidepressant drug). We reasoned that both the amino group and the cyclopropane ring would be protonated in the

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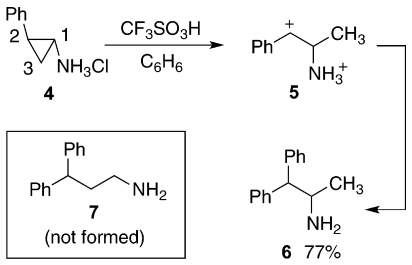
superacid, leading to the formation of a reactive dicationic superelectrophile.[13] When compound **4** was reacted with benzene in the presence of the Brønsted superacid CF_3SO_3H (triflic acid), ring opening occurred to provide the addition product **6** in good yield (Scheme 2). The structure of the product was verified by full characterization including DEPT NMR analysis. This conversion may be explained by protolytic ring opening of **4** to give 1,3-dication **5**. Superelectrophile **5** then reacts with benzene to eventually provide compound **6**. The formation of product **6** involves regioselective protonation at the distal (C_2–C_3) bond rather than the vicinal (C_1–C_2) bond of the cyclopropane ring. Protolytic cleavage of the vicinal bond would produce a more stable benzylic 1,4-dication (vide infra), leading to product **7**, but this was not observed.

Scheme 2. Superacid-Promoted Ring Opening of Cyclopropane 4



In order to probe the regiochemistry of this cyclopropane ring-opening reaction, we performed theoretical calculations involving geometry optimizations at the M06/6-31+G(d,p) level of theory using the Jaguar program suite[14] followed by single-point energy calculations at the M06/cc-pvtz(-f) level (Figure 1). Energy values were calculated from the optimized structures using the PBF solvent continuum model (triflic acid solvent sphere) with a specific triflic acid as the protonating agent. Protonation of the cyclopropane ring can give two isomeric dications, 1,4-dication **9** and 1,3-dication **12**. It has been previously shown that increasing the charge separation tends to stabilize dicationic species.[15] As a result, 1,4-dication **9** was found to be 5.7 kcal/mol more stable than 1,3-dication **12**. Nevertheless, reaction in superacid led to the exclusive formation of the 1,3-dication (i.e., **12**) and subsequently gave product **6** by Friedel–Crafts reaction with benzene (Scheme 3). The reaction course may be understood, however, by considering the energies of the respective transition states (**10** and **11**). Transition state **10** leading to protolysis of the C_1–C_2 bond was found to be 28.7 kcal/mol above the starting monocation **8**, while transition state **11** leading to protolysis of the distal (C_2–C_3) bond was found to be 22.2 kcal/mol above monocation **8**. Thus, transition state **11** is 6.5 kcal/mol more stable than transition state **10**. With the lower energy barrier leading to dication **12**, this becomes the kinetically preferred reaction path. An examination of the transition-state structures **10** and **11** revealed that protolysis of the distal bond to give **11** provides a structure with a larger distance between the ammonium charge and the developing carbocation charge. In structure **11**, the distance between the ammonium nitrogen and the incoming proton (from triflic acid) was found to be 3.6 Å, while in structure **10**, the distance between the ammonium nitrogen and the incoming proton was found to be 2.3 Å.[16] In order to rule out steric effects for the regioselectivity of protonation, calculations were also done without the triflate anion. Even without triflate, distal bond cleavage was preferred over vicinal bond cleavage by about 5.0 kcal/mol.

As expected from previous theoretical calculations,[10] the distal (C_2–C_3) bond is lengthened prior to protonation relative to the vicinal bonds. For cation **8**, the length of the distal (C_2–C_3) bond is estimated to be 1.510 Å, while the lengths of the vicinal bonds are 1.502 Å (C_1–C_2) and 1.483 Å (C_1–C_3). Clark and Schleyer previously noted that the longest cyclopropane bond is generally the bond most easily cleaved.[10a] To further support this, we also calculated the natural atomic orbital bond orders of **8**, which were found to be 0.817 (C_2–C_3), 0.828 (C_1–C_2), and 0.830 (C_1–C_3). Taken together, these results suggest that the observed distal bond cleavage is the result of two effects: lengthening and weakening of the (C_2–C_3) bond by the σ-acceptor properties of the ammonium group and the charge–charge repulsive effects in the transition states leading to ring opening. Ring opening is of course initiated by protonation.

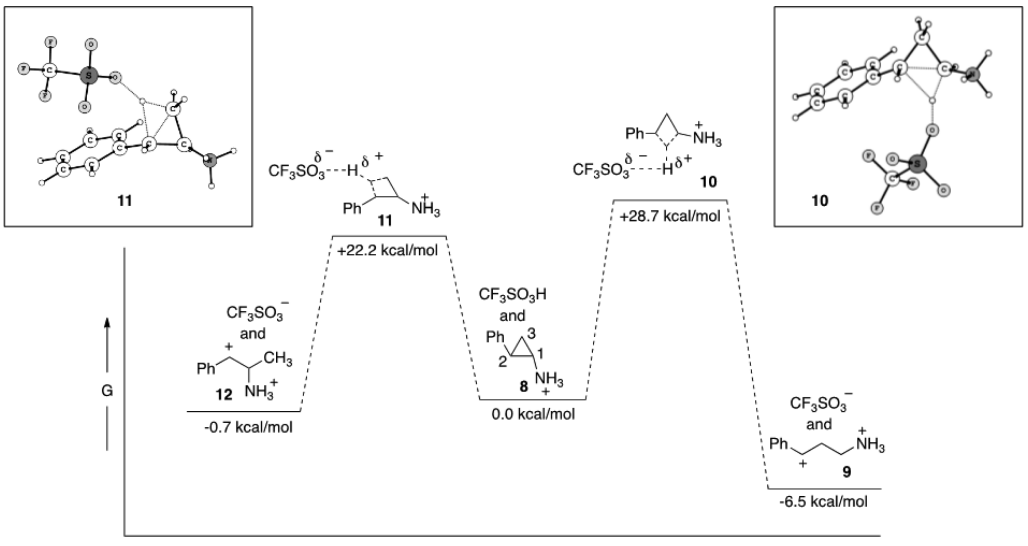


Figure 1. Calculated relative free energies in solution for distal (**8** → **11** → **12**) and vicinal (**8** → **10** → **9**) ring-opening reactions involving cyclopropane **8** and transition-state structures **10** and **11**.

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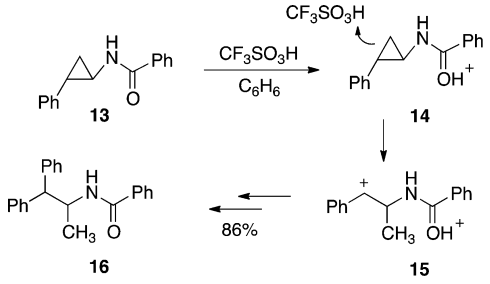
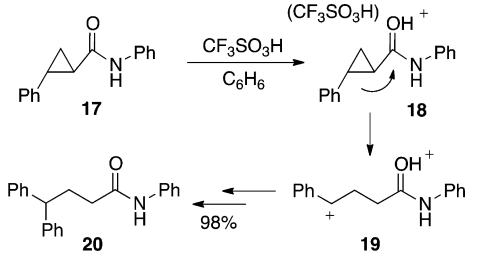
Scheme 3. Superacid-Promoted Ring Opening of Cyclopropane 13



A similar reaction was seen in the ring-opening chemistry of an amide derivative of tranylcypromine. When compound **13** was reacted with benzene in superacid, compound **16** was formed as the exclusive product (Scheme 3). This conversion likely involves formation of ion **14** followed by protonation at the distal C_2-C_3 bond to give dication **15**. Electrophilic reaction with benzene and deprotonation would then give the final product **16**. In contrast, the isomeric amide **17** derived from 2-phenylcyclopropane carboxylic acid was ring-opened by cleavage of the vicinal C_1-C_2 bond of the cyclopropane ring (Scheme 4). This reaction also involves protonation of the

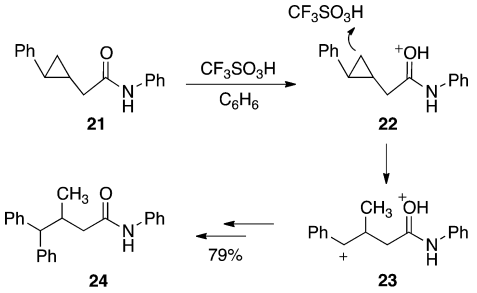
Scheme 4. Superacid-Promoted Ring Opening of Cyclopropane 17

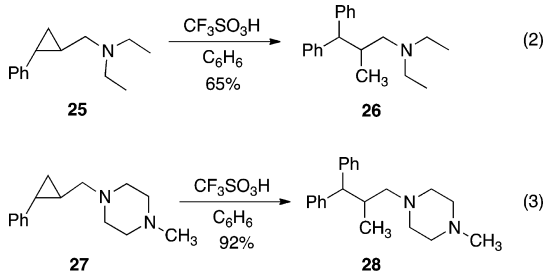


amide carbonyl bond, giving cation **18**, although diprotonation of the amide may also be possible in the superacidic medium.[13] In either case, the resulting carboxonium ion should possess a low-lying carbonyl LUMO, which should trigger the opening of the vicinal C_1-C_2 bond and result in the formation of dication **19**. The reaction with benzene then provides the final addition product **20**. Although amides **13** and **17** are similar in structure, they undergo ring-opening reactions by two distinctly different mechanisms.

Like other cyclopropanes having strong π-acceptor groups, the amide group of **17** (and its carboxonium ion **18**) interacts with 3e′ orbital of the cyclopropane ring, leading to lengthening and cleavage of the vicinal C_1-C_2 bond. Interestingly, the same reaction with homologue **21** leads to cleavage of the distal C_2-C_3 bond and formation of product **24** (Scheme 5). Thus, the reaction with CF_3SO_3H leads to the formation of carboxonium ion **22**. Because the carboxonium group is no longer in conjugation with the cyclopropane ring, the protonated amide is not a π-acceptor group but rather is a cationic σ-acceptor group. This leads to an interaction with the cyclopropane 1e″ orbital and lengthening of the distal C_2-C_3 bond with electrophilic and nucleophilic reaction at this site. Following protonation of the distal C_2-C_3 bond, superelectrophile **23** is formed, and Friedel–Crafts reaction gives the final product **24**. In a similar respect, the amine and piperazine derivatives (**25** and **27**) exhibit ring opening at the distal C_2-C_3 bond of the cyclopropane ring (eqs 2 and 3). This leads to the respective Friedel–Crafts products **26** and **28**.

Scheme 5. Superacid-Promoted Ring Opening of Cyclopropane 21





In summary, we have found unusual examples of distal bond cleavage in several cyclopropane systems having a cationic σ-acceptor group. The results are consistent with earlier observations that σ-acceptor groups lengthen the distal bond of cyclopropane rings. Theoretical calculations also indicate that ring opening is a kinetically controlled process in which charge–charge repulsive effects in the transition-state structures may be important.

EXPERIMENTAL SECTION

General. All of the reactions were performed using oven-dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid was freshly distilled prior to use. All commercially available compounds and solvents were used as received. ^{1}H NMR and ^{13}C NMR spectra were obtained using a 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, while high-resolution mass spectra were obtained from a commercial analytical laboratory (electron impact ionization; sector instrument analyzer type).

1-Methyl-2,2-diphenylethylamine (6). In a vented flask or vial (CAUTION: venting is necessary because the superacid protonates the chloride, generating HCl gas and modest internal pressure), salt **4** (0.1 g, 0.59 mmol) was suspended in 1 mL of anhydrous benzene, to which was added CF_3SO_3H (1.0 mL, 1.9 mmol). The mixture was stirred at 25 °C for 4–6 h, after which the solution was poured over several grams of ice. Chloroform (30 mL) was poured into the mixture, and the aqueous phase was made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase was followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts were washed with H_2O and then brine (twice). Following a drying step (Na_2SO_4), filtration, and removal of solvent, compound **6**[17] was isolated (oil, 0.096 g, 0.45 mmol).

***N*-(1,1-Diphenylpropan-2-yl)benzamide (16).** Compound **4** (0.2 g, 1.18 mmol) was partitioned between dichloromethane (15 mL) and 1.0 M NaOH (15 mL) in a separatory funnel. Extraction of the free amine was followed by drying of the organic solution with

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Na_2SO_4. The resulting solution was filtered directly into a reaction flask, to which was added triethylamine (0.2 mL, 1.43 mmol) and benzoyl chloride (0.14 mL, 1.18 mmol). The solution was stirred for 2 h and then washed with 1.0 M HCl, water, and brine (twice). Further purification with silica gel chromatography (ether/hexanes) provided known cyclopropylamide **13**.[18]

Amide **13** (0.1 g, 0.42 mmol) was suspended in 1 mL of anhydrous benzene, to which was added CF_3SO_3H (1.0 mL, 1.9 mmol). The mixture was stirred at 25 °C for 4−6 h, after which the solution was poured over several grams of ice. Chloroform (30 mL) was poured into the mixture, and the aqueous phase was made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase was followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts were washed with H_2O and then brine (twice). Following a drying step (Na_2SO_4), filtration, removal of solvent, and silica gel chromatography (ether/hexanes), compound **16**[19] was isolated (0.114 g, 0.36 mmol) as a light-yellow solid. Mp: 163−164 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.27 (d, J = 6.5 Hz, 3H), 4.03 (d, J = 9.4 Hz, 1H), 5.07−5.13 (m, 1H), 7.18−7.25 (m, 2H), 7.31−7.39 (m, 8H), 7.45 (tt, J = 1.2, 7.4 Hz, 1H), 7.48−7.53 (m, 3H), 7.62 (tt, J = 1.8, 7.4 Hz, 1H)7.83−7.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.4, 48.0, 58.1, 126.6, 126.8, 128.3, 128.5, 128.7, 130.1, 131.2, 132.4, 135.0, 137.6, 141.7, 142.1, 166.9. Low-resolution MS (EI) m/z: 315 (M^+), 194, 167, 165, 148, 105. HRMS (EI) m/z: calcd for $C_{22}H_{21}NO$, 315.16232; found, 315.16253.

***N*-(3,3-Diphenylpropyl)benzamide (20).** *trans*-2-Phenylcyclopropane-1-carbonyl chloride (0.2 g, 1.1 mmol) was dissolved in anhydrous dichloromethane (10 mL), and the solution was cooled in an ice bath. To this solution, aniline (0.25 mL in 5 mL dichloromethane) was added slowly. The mixture was stirred for 2 h and then washed with 1.0 M HCl, water, and brine (twice). Further purification with silica gel chromatography (ether/hexanes) provided known cyclopropylamide **17**.[20]

Amide **17** (0.1 g, 0.42 mmol) was suspended in 1 mL of anhydrous benzene, and CF_3SO_3H (1.0 mL, 1.9 mmol) was added. The mixture was stirred at 25 °C for 4−6 h, after which the solution was poured over several grams of ice. Chloroform (30 mL) was poured into the mixture, and the aqueous phase was made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase was followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts were washed with H_2O and then brine (twice). Following a drying step (Na_2SO_4), filtration, removal of solvent, and silica gel chromatography (ether/hexanes), compound **20** was isolated (0.13 g, 0.41 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.32 (t, J = 7.9 Hz, 2H), 2.48−2.55 (m, 2H), 3.99 (t, J = 7.8 Hz, 1H), 7.18−7.41 (m, 13H), 7.64 (d, J = 7.7 Hz, 2H), 8.27 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 31.2, 35.9, 50.6, 120.3, 124.3, 126.5, 128.0, 128.7, 129.0, 138.3, 144.3, 171.8. Low-resolution MS (EI) m/z: 315 (M^+), 178, 167, 165, 152, 135, 105, 93, 92. HRMS (EI) m/z: calcd for $C_{22}H_{21}NO$, 315.16232; found, 315.16280.

***N*-Phenyl-2-(2-phenylcyclopropyl)acetamide (21).** (*E*)-4-Phenylbut-3-enoic acid (0.162 g, 1.0 mmol), aniline (0.09 mL,1 mmol), EDCI (0.23 g, 1.2 mmol), and DMAP (0.05 g, 0.4 mmol) were dissolved in anhydrous dichloromethane (20 mL). The solution was stirred for 12 h at 25 °C, after which it was partitioned between cold water and $CHCl_3$. The organic layer was separated, washed with H_2O (twice) and brine (twice), and dried over anhydrous sodium sulfate. The crude product was isolated, and further purification by column chromatography (hexane/ethyl acetate) gave the known amide (*E*)-*N*,4-diphenylbut-3-enamide.[21]

According to a published procedure, a stirred solution of (*E*)-*N*,4-diphenylbut-3-enamide (0.237 g, 1.0 mmol) was prepared with anhydrous dichloromethane (15 mL), and diethylzinc (1.0 M in hexane, 2.5 mL, 2.5 mmol) was then added at −20 °C under an argon atmosphere. After 10 min, diiodomethane (0.25 mL, 3 mmol) was slowly added to the mixture. Stirring was continued for 10 h. A saturated NH_4Cl solution was then added to the mixture, and the resulting solution was extracted with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Silica gel column chromatography (2:1 hexanes/ethyl acetate) provided a colorless solid (0.228 g, 91%). Mp: 80−81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97−1.03 (m, 1H), 1.08−1.14 (m, 1H), 1.44−1.53 (m, 1H), 1.82−1.88 (m, 1H), 2.52 (dd, J = 5.2, 9.7 Hz, 1H), 3.36 (s, 1H), 7.11−7.14 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.20−7.28 (m, 1H), 7.30−7.38 (m, 4H), 7.66 (d, J = 7.6 Hz, 2H), 8.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.8, 19.5, 23.1, 41.9, 120.3, 124.3, 125.8, 125.9, 128.5, 129.0, 138.3, 142.4, 171.1. Low-resolution MS (EI) m/z: 251 (M^+), 193, 160, 117, 93, 91, 77. HRMS (EI) m/z: calcd for $C_{17}H_{17}NO$, 251.13102; found, 251.13120.

3-Methyl-*N*,4,4-triphenylbutanamide (24). Compound **21** (0.251 g, 1.0 mmol) was dissolved in benzene (3 mL), and CF_3SO_3H (3 mL, 34 mmol) was added slowly with stirring. The reaction mixture was stirred overnight at room temperature and then poured over several grams of ice. Chloroform (ca. 30 mL) was then added, and the aqueous layer was made basic with 10 M NaOH. Separation of the organic phase was followed by washing with water and then saturated brine (twice). The organic solution was dried with Na_2SO_4 and then concentrated in vacuo. Further purification with silica gel column chromatography (2:1 hexanes/ethyl acetate) yielded compound **24** as a colorless oil (0.26 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (d, J = 6.6 Hz, 3H), 2.04 (dd, J = 4.5 Hz, 1H), 2.49 (dd, J = 3, 14.5 Hz, 1H), 3.02−3.13 (m, 1H), 3.58 (d, J = 11.1 Hz, 1H), 7.15−7.40 (m, 13H), 7.62 (d, J = 7.8 Hz, 2H), 8.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.9, 34.3, 43.5, 58.8, 120.2, 124.3, 126.3, 126.5, 128.0, 128.6, 128.8, 129.0, 138.2, 143.7, 143.8, 171.5. Low-resolution MS (EI) m/z: 329 (M^+), 194, 167, 165, 135, 115, 92, 77. HRMS (EI) m/z: calcd for $C_{23}H_{23}NO$, 329.17797; found, 329.17821.

***N*,*N*-Diethyl-2-methyl-3,3-diphenylpropan-1-amine (26).** Compound **25** was prepared using a published procedure.[22] Amine **25** (0.1 g, 0.49 mmol) was suspended in 1 mL of anhydrous benzene, to which was added CF_3SO_3H (1.0 mL, 1.9 mmol). The mixture was stirred at 25 °C for 4−6 h, after which the solution was poured over several grams of ice. Chloroform (30 mL) was poured into the mixture, and the aqueous phase was made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase was followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts were washed with H_2O and then brine (twice). Following a drying step (Na_2SO_4), filtration, removal of solvent, and silica gel chromatography (ether/hexanes), known compound **26** was isolated (0.090 g, 0.32 mmol) as an oil.[23]

1-Methyl-4-(2-phenylcyclopropylmethyl)piperazine (27). Compound **27** was prepared using a published synthetic method[23] and isolated as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.76−0.80 (m, 1H), 0.90−0.94 (m, 1H), 1.19−1.23 (m, 1H), 1.63 (pent, J = 4.9 Hz, 1H), 2.24 (s, 3H), 2.31 (q, J = 6.6 Hz, 2H), 2.37−2.42 (m, 4H), 2.50 (q, J = 6 Hz, 4H), 6.99−7.01 (m, 2H), 7.07−7.11 (m, 1H), 7.20 (t, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.0, 20.7, 22.7, 46.1, 53.1, 55.1, 63.0, 125.4, 125.6, 128.3, 142.8. Low-resolution MS (EI) m/z: 230 (M^+), 229, 215, 139, 91, 70. HRMS (EI) m/z: calcd for $C_{15}H_{22}N_2$, 230.17830; found, 230.17855.

1-Methyl-4-(2-methyl-3,3-diphenylpropyl)piperazine (28). Amine **27** (0.102 g, 0.43 mmol) was suspended in 1 mL of anhydrous benzene, to which was added CF_3SO_3H (1.0 mL, 1.9 mmol). The mixture was stirred at 25 °C for 4−6 h, after which the solution was poured over several grams of ice. Chloroform (30 mL) was poured into the mixture, and the aqueous phase was made basic (pH paper) by slow addition of 10 M NaOH. Extraction and separation of the organic phase was followed by a second chloroform extraction (30 mL) of the aqueous phase. The combined chloroform extracts were washed with H_2O and then brine (twice). Following a drying step (Na_2SO_4), filtration, removal of solvent, and silica gel chromatography (ether/hexanes), compound **28** was isolated (0.123 g, 0.0004 mmol) as a light-brown solid. Mp: 141−142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.95 (d, J = 6.5 Hz, 3H), 2.13 (dd, J = 3.1, 10.8 Hz, 1H), 2.28 (dd, J = 4.4, 12.4 Hz, 1H), 2.40−2.45 (m, 3H), 2.61−2.67 (m, 8H), 3.70 (d, J = 9.6 Hz, 1H), 7.18−7.33 (m, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.4, 34.3, 45.4, 52.6, 54.9, 56.8, 63.2, 126.1, 126.1, 128.0, 128.4, 128.5, 143.9, 144.2. Low-resolution MS (EI) m/z: 308 (M^+), 252, 193, 167,

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165, 113, 70. HRMS (EI) m/z: calcd for $C_{21}H_{28}N_2$, 308.22525, found 308.22471.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra, and computational procedures and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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