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Experimental and Theoretical Studies of a One-Flask Synthesis of 3*H*-1-Benzazepines from 2-Haloanilines and α,β-Unsaturated Ketones

Keith Ramig,*[a] Edyta M. Greer,*[a] David J. Szalda,[a] Rabail Razi,[a] Fahima Mahir,[a] Nataliya Pokeza,[a] Wei Wong,[a] Benjamin Kaplan,[a] Joanne Lam,[a] Ayesha Mannan,[a] Christopher Missak,[a] Dat Mai,[a] Gopal Subramaniam,[b] William F. Berkowitz,[b] Prakash Prasad,[b] Sasan Karimi,[c] Ngai Hin Lo,[c] and Linas V. Kudzma[d]

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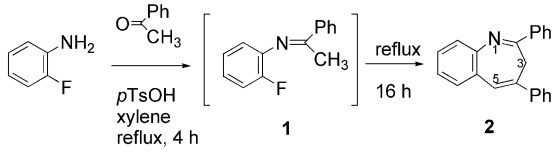
3*H*-1-Benzazepines are prepared in one step from the reaction of 2-fluoro- or 2-chloroaniline and several aryl vinyl ketones. Enones **9a–c** gave benzazepines **11a–c** as expected, showing that alkyl substitution at C4 and C5 in the benzazepines is possible. However, enone **9d** underwent decomposition due to conjugate addition of the 2-fluoroaniline, while enone **10** gave unsaturated imine **12** as the only product able to be isolated. The failure of unsaturated imine **12** to undergo cyclization may indicate that placement of an alkyl group at C3 of the benzazepines may not be possible. Isolation of by-products buttressed by a computational study verifies a postulated multi-step process for benzazepine formation: a [1,5] sigmatropic shift in fluoroimine **3**, addition elimination to give carbocation **15**, formation of the unstable 5*H*-1-benzazepine **7**, and acid-catalyzed isomerization to give the stable 3*H*-1-benzazepine **2**. The calculations also indicate why unsaturated imine **12** fails to cyclize. NMR spectroscopic experiments show that the 3*H*-benzazepines undergo fast conformational exchange on the NMR time scale at room temperature except when there is an alkyl substituent at C5.

Introduction

The 1-benzazepine moiety is being found more and more frequently in molecules of pharmaceutical interest.[1] Although there are scattered accounts of 3*H*-1-benzazepines[2] their syntheses are laborious and their chemistry has not been well studied. A preliminary report from our labs[3] described a new synthesis of 3*H*-1-benzazepines using a one-flask procedure (Scheme 1). Acetophenone was heated with one equivalent of 2-fluoroaniline, with azeotropic removal of water, forming the imine **1**.[4] Further heating yielded 2,4-diphenyl-3*H*-1-benzazepine **2**. We are aware of only one other report[2c] of this kind of process, which gives very low yields of benzazepines from two exotic highly fluorinated aromatic amines and acetophenone.



Scheme 1.

We will disclose here new findings which will allow production of a wider variety of 3*H*-1-benzazepines. Possible mechanisms for benzazepine formation will be proposed, based partially on new experimental data and calculations. Also, fluxional behavior of the azepine ring will be studied with NMR spectroscopic experiments.

From our previous work,[3] it appeared that only 2,4-diarylbenzazepines could be prepared, as both 4-methyl-2-pentanone and propiophenone failed to give benzazepines under the usual conditions. Also, the two aryl groups in the cases which do work must perforce be identical to each other. These circumstances lead to another limitation: The 3- and 5-positions will remain unsubstituted in every benzazepine. Herein we will show that the limitations are not as severe as we had at first thought.

Initial Mechanistic Hypothesis

The mechanism for benzazepine formation that we originally proposed[3] is shown in Scheme 2. After acid-catalyzed

[a] Department of Natural Sciences, Baruch College of the City University of New York,
17 Lexington Ave., New York, NY 10010, USA
Fax: +1-646-660-6201
E-mail: keith.ramig@baruch.cuny.edu
edyta.greer@baruch.cuny.edu
[b] Department of Chemistry and Biochemistry, Queens College of the City University of New York,
65-30 Kissena Blvd., Flushing, NY 11367, USA
[c] Department of Chemistry, Queensborough Community College of the City University of New York,
222-05 56th Ave., Bayside, NY 11364, USA
[d] Baxter Anesthesia and Critical Care,
95 Spring St., New Providence, NJ 07974, USA

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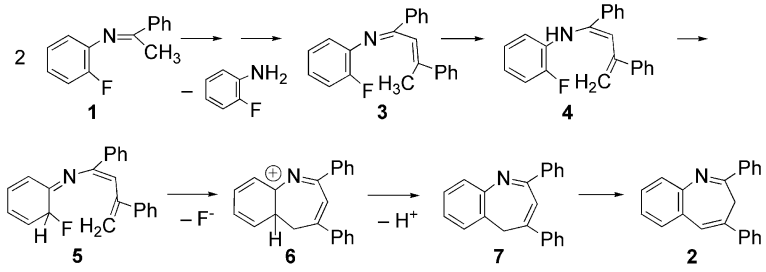


Scheme 2.

formation of imine **1**, further heating may cause an aldol-like condensation between two imines, giving unsaturated imine **3**. Imines are known to undergo this kind of transformation under similar conditions.[5] After proton transfer giving compound **4**, further rearrangement produces intermediate **5**. This could undergo acid-catalyzed cyclization accompanied by fluoride loss, giving cation **6**, which rearomatizes to 5*H*-benzazepine **7** by proton loss. Finally, benzazepine **7** isomerizes to benzazepine **2**.

We have failed in attempts to isolate unsaturated imine **3**, with which we had hoped to study the proposed conversion to later intermediates and the benzazepine. All attempts at heating simple imine **1** in order to bring about the aldol-like condensation either gave no reaction, or with longer heating or a higher temperature, caused conversion to benzazepine **2**. We will reveal here new experiments that give strong evidence that the mechanism does indeed proceed through unsaturated imine **3**, and will propose an alternative mechanism upon which calculations have been performed.

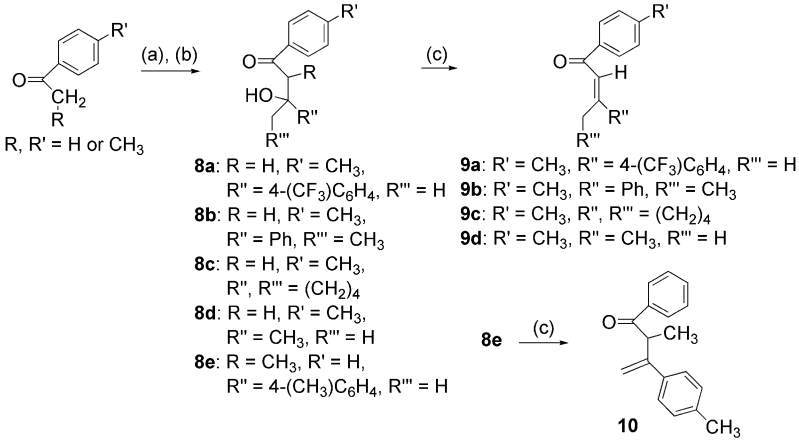
Results and Discussion

Generalization Studies

If the imine **3** from Scheme 2 is indeed an intermediate leading to the benzazepines, then it should be possible to prepare benzazepines using the imine formed from 2-fluoroaniline and an α,β-unsaturated ketone We have found that dypnone (the self-aldol/dehydration product of acetophenone) will react with two equivalents of 2-fluoroaniline to give benzazepine **2** in good yield. Presumably the intermediate in this process is imine **3**.

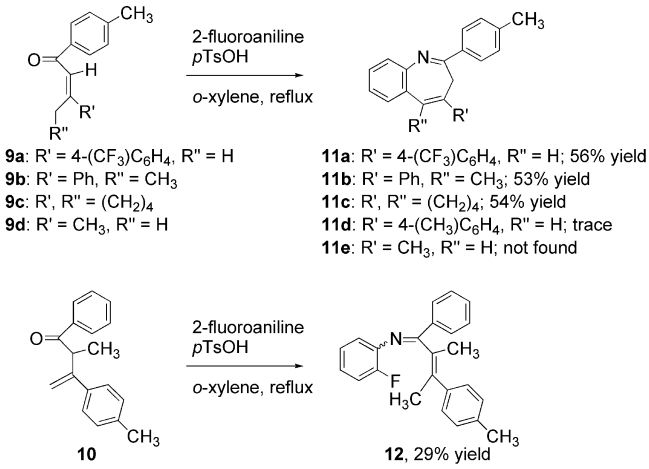
We explored the possibility of varying the substituents on the benzazepine skeleton, by using various dypnone derivatives in the reaction. First, the aldols **8a**–**e** were prepared in 35–60% yields from the enol ethers of either 4′-methylacetophenone or propiophenone, and a different ketone (Scheme 3).[6] All the aldols were stable except for **8d**, which partially dehydrated in the crude reaction mixture. Then, the aldols **8a**–**d** were dehydrated[7] uneventfully to give enones **9a**–**d** in 35–72% yields. Aldol **8e** however, gave the β,γ-unsaturated ketone **10** in 41% yield.

Treatment of the enones **9a**–**c** and **10** with 1.5 to two equivalents of 2-fluoroaniline and a catalytic amount of *p*TsOH delivered 3*H*-1-benzazepines **11a**–**c** in moderate yields (Scheme 4). Enone **10** gave unsaturated imine **12** as the only isolable product; the bulk of the crude reaction mixture consisted of many unidentified products, none of which appeared to be a benzazepine, judging by NMR spectroscopic analysis. Enone **9d** gave a complex mixture of products, with no evidence for the presence of benzazepine **11e**. The only product able to be identified was a small amount of benzazepine **11d**.[3] We theorize that decomposition of the enone is initiated by conjugate addition of 2-fluoroaniline, resulting in a retro-aldol-like reaction. This



Scheme 3. (a) TMSCl, NaI, triethylamine, in CH_3CN; (b) ketone [**a**: 4′-(trifluoromethyl)acetophenone, **b**: acetophenone, **c**: cyclohexanone, **d**: acetone, **e**: 4′-methylacetophenone], $TiCl_4$ in CH_2Cl_2; (c) TFAA, triethylamine, DMAP, in CH_2Cl_2.

would yield 4′-methylacetophenone as one of the products, which would react with remaining 2-fluoroaniline and give benzazepine **11d**. This taught us that the β position of the enone needs to be sufficiently sterically hindered to avoid side-reactions. Enone **9c**, which is more hindered at the β carbon than **9d**, furnished benzazepine **11c** in acceptable yield.



Scheme 4.

Benzazepine **11b** gave crystals suitable for X-ray structural analysis. Intensity measurements and systematic absences were consistent with the monoclinic space group $P2_1/c$ and it was used for the solution and refinement of the structure. The structure was solved by direct methods.[8] The carbon atoms and nitrogen atom were refined using anisotropic thermal parameters. Hydrogen atoms were located on a difference Fourier map and refined with individual isotropic thermal parameters. An empirical absorption correction was applied using ABSOR.[9] A view of the structure is found in Figure 1 and crystallographic details are provided in the Supporting Information. In the seven-membered ring, C2, C4, C6, and C7 form a best fit plane with a RMS deviation of 0.02 Å (C3 is 0.9 Å below this plane while N1 and C5 are each 0.4 Å above the plane). The phenyl ring labeled C21–C26 makes an angle of 31.3° with this plane and the phenyl ring labeled C41–C46 makes an angle of 84.4° with the plane. There are two intermolecular C–H···N hydrogen bonds[10] one between the hydrogen atom on C45 and the nitrogen atom on a symmetry-related molecule H45···N1A 2.74 Å with a C45–H45···N1A (A = x, 0.5 – y, –0.5 + z) angle of 165° and the other C241–H241···N1B with a H241···N1B distance 2.902 Å and angle of 168° (B = 1 – x, –0.5 + y, 0.5 – z). We are aware of one other report of the crystal structure of a related benzazepine.[11]

Attempts were made to optimize the yield of the benzazepines. Initially it was thought that use of two equivalents of 2-fluoroaniline was necessary, because when the starting ketone is acetophenone as in Scheme 2, little or no benzazepine is formed without inclusion of the extra 2-fluoroaniline. But later we found that one equivalent is sufficient when the starting material is a dypnone derivative, although

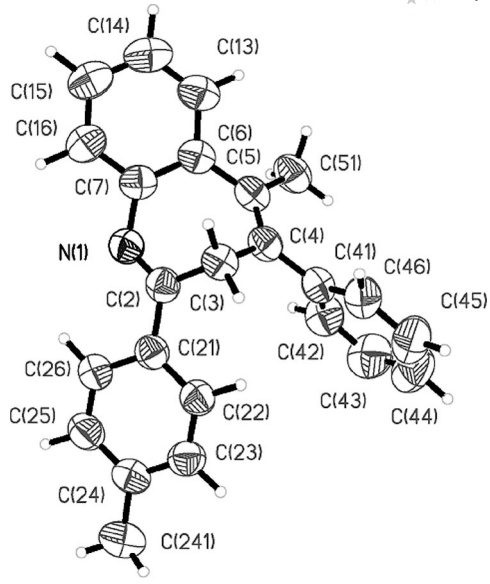


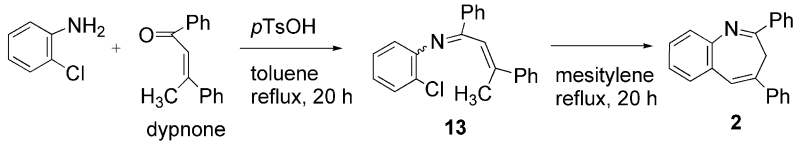
Figure 1. An ORTEP drawing of **11b** with thermal ellipsoid at 50%.

the yield of benzazepine is diminished by about 15% and starting enone remains. The optimal amount appears to be 1.5 equiv.; the yield of benzazepine **11a** improved from 44% when two equivalents were used, to 56% when 1.5 equiv. were used.

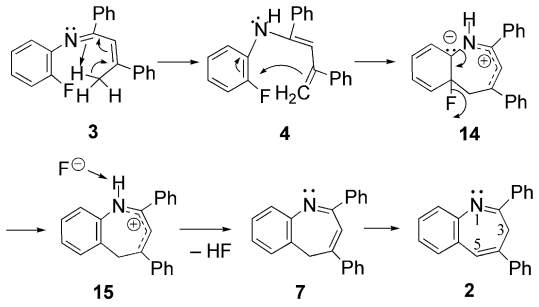
An Alternative Mechanistic Hypothesis

In the preliminary communication,[3] we reported that 2-chloroaniline failed to give benzazepine under conditions where 2-fluoroaniline would. We have reinvestigated this result, and have found that when the solvent is toluene at reflux, 2-fluoroaniline is indeed more reactive towards dypnone than 2-chloroaniline; in the former case, conversion to benzazepine is far along while in the latter case, little or no benzazepine is formed. However, when the solvent is the higher-boiling *o*-xylene at reflux, both anilines give a good yield of benzazepine. Building on this, we have been successful in preparing the chloro analog of fluoroimine **3**, namely chloroimine **13** (Scheme 5). When chloroimine **13** is heated at reflux in mesitylene, *with or without the acid catalyst*, benzazepine **2** is formed. While this latter step does not depend on the presence of *p*TsOH, we have performed the proper controls to show that formation of imine does require acid catalysis.

The fact that imine **13** can be converted to benzazepine without the presence of an extra equivalent of 2-chloroaniline to neutralize the HCl that is presumably formed, is also a significant finding. A mechanism that fits all the current data is presented in Scheme 6. The conversion of fluoroimine **3** to enamine **4** could occur by a thermal [1,5] sigmatropic shift. Then, an addition-elimination process ensues. Enamine **4** gives ylide **14**, which ejects a halide ion to give carbocation **15**. We also considered an intramolecular [4+2] cycloaddition of **4**, which would give a ring-fused aziridine.



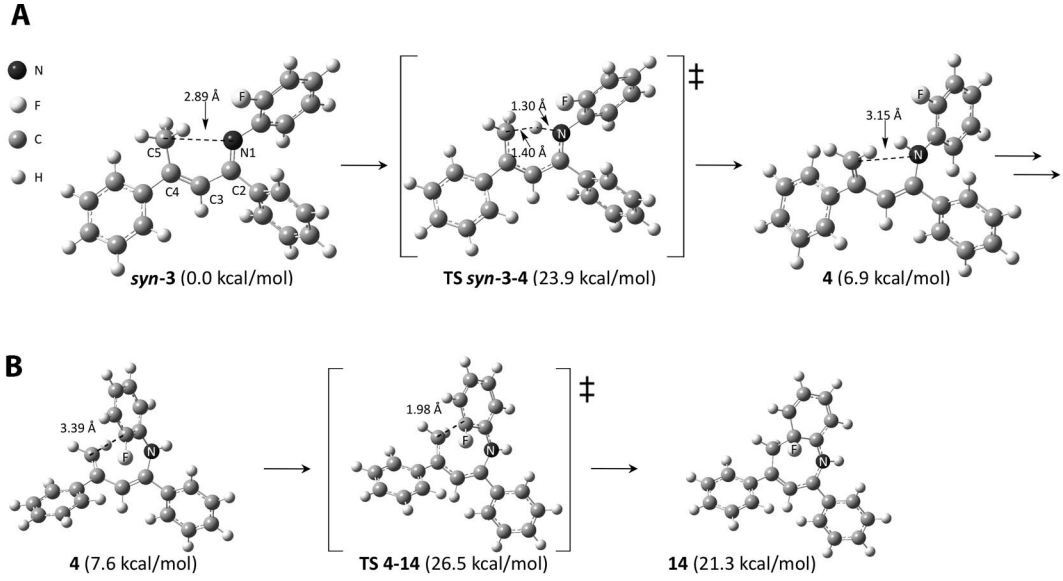
Scheme 5.



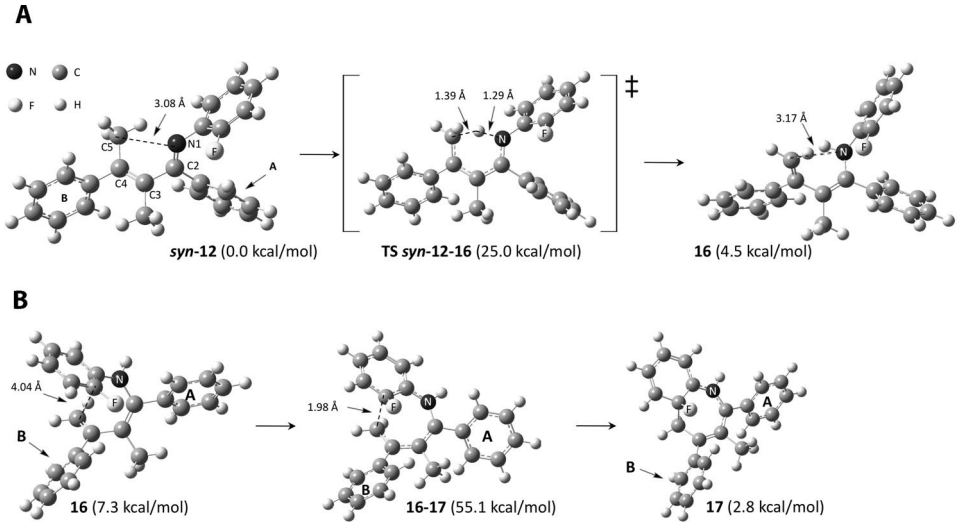
Scheme 6.

At this point, we began a computational study, with the dual aim of verifying the mechanism of Scheme 6, and to explain the failure of imine **12** to undergo cyclization. Scheme 7 shows two steps of Scheme 6: (A) the proton transfer from fluoroimine *syn*-**3** to fluoroamine **4** and (B) the cyclization of amine **4** to ylide **14**. All the molecules shown in Scheme 7 are structural isomers, thus we were able to compare both processes on the same energy scale. We found that, at the B3LYP/6-31G(d) level, a 23.9 kcal/mol saddle point (**TS3**–**4**) connects **3** and **4** which represents a proton shift from C5 to N1. We chose the B3LYP/6-31G(d) combination of the method and the basis set because it performed well in predicting the bond lengths and bond angles of **11b** determined by X-ray analysis.[12] Next, a reaction path was computed for converting amine **4** to ylide **14**.[13] The barrier height of **TS4**–**14** is 26.5 kcal/mol and reaches **14** in a reaction that is endothermic by 21.3 kcal/mol. Both activation energies are attainable in refluxing xylene. The calculations also showed that an intramolecular [4+2] cycloaddition in **4**, giving a tryclic aziridine, is highly unlikely as the activation energy was found to be prohibitively high at 65.0 kcal/mol.[12]

Next, we sought to explain the failure of imine **12** to cyclize. We investigated this system by taking points corresponding to the proton transfer from fluoroimine *syn*-**3** to enamine **4**, and cyclization of **4** shown in Scheme 7, replacing the hydrogen atom at C-3 by a methyl group and reoptimizing. A different result from Scheme 7 was obtained, which is summarized in Scheme 8. After reoptimizing the structures, we found that, at the B3LYP/6-31G(d) level, the proton transfer from imine **12** to yield **16** involves **TS12**–**16**. The barrier height of **TS12**–**16** is 25.0 kcal/mol so the [1,5] sigmatropic proton shift between C5 and N1 is feasible under the reaction conditions. Then we attempted, but were unable, to find a cyclization route to convert **16** to **17**. We identified structure **16**–**17** that was characterized by the frequency calculations as the third-order saddle-point due to strong geometric distortion caused by the methyl group at C3 sandwiched between phenyl rings A and B. The structure **16**–**17** is located 55.1 kcal/mol above imine **12** and is therefore unreachable under the applied experimental reaction conditions. So the problem appears to be steric interactions between the methyl group at C-3 and the phenyl rings.

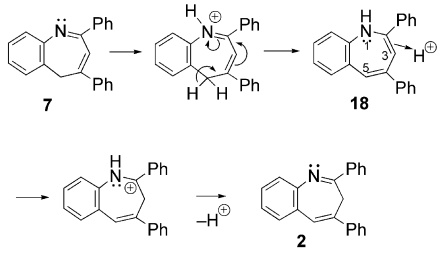


Scheme 7. **A**: Computed proton transfer between C5 and N1 of fluoroimine **3** and fluoroamine **4**. **B**: cyclization of fluoroimine **4**; comparison on the same energy scale. Bond lengths are given in Å. Energies in parentheses calculated at the B3LYP/6-31G(d) level include ZPE corrections.



Scheme 8. **A**: Computed proton transfer from imine **12** to amine **16**. **B**: Cyclization of amine **16**. For the simplicity of calculations the methyl group in the *para* position of ring B was eliminated in **12** and related computed structures. Energies include ZPE corrections.

We now turn to elucidating the rest of the mechanism of Scheme 6. At the time of our initial study,[3] we supposed the existence of 5*H*-benzazepine **7** without any supporting experimental evidence. Careful inspection of the crude reaction mixture reveals the presence of **7**, in a 1:12 ratio with the 3*H*-isomer **2** as judged by ^{1}H NMR integration values of the two singlets due to the methylene groups. Chromatographic purification gave pure 5*H*-isomer **7**. The two benzazepine isomers equilibrate in the presence of an acid catalyst. When either 5*H*-isomer **7** or 3*H*-isomer **2** is heated in xylene in the presence of a catalytic amount of *p*TsOH, a 1:12 mixture of the two isomers results, favoring the 3*H* isomer. We have also found that equilibration can occur without the presence of added acid, albeit at a slower rate, and is almost squelched by addition of DMAP. These results point to acid catalysis by the glass surface of the reaction flask. The possibility of interconversion of isomers **7** and **2** by two distinct series of [1,5] sigmatropic proton shifts was ruled out by calculations. Our calculations showed that the energy barrier corresponding to the sequence starting with the proton transfer from C5 to C2 is very high, at 48 kcal/mol. In the case of the sequence that begins with the proton transfer from C5 to N1 the activation barrier is 42.5 kcal/mol.[12] Therefore we favor a mechanism which starts with protonation of the nitrogen atom of 5*H*-isomer **7** and proton loss to give the 1*H*-isomer **18** (Scheme 9). This isomer then undergoes a similar protonation/deprotonation sequence, delivering 3*H*-isomer **2**. (It is also possible that 1*H*-isomer **18** could be formed directly from carbocation **15** by loss of a proton from C5.) While we have no direct evidence for the involvement of the 1*H*-isomer **18**, calculations show that it is the least stable of the three (8.4 kcal/mol less stable than **2**), followed by the 5*H* isomer (2.0 kcal/mol less stable than **2**), with the 3*H* isomer being the most stable (Figure 2). Hence the 1*H* isomer may be present in an amount too small to be easily detected. Or, it is also possible that the site of initial protonation of the 5*H* isomer could be C3, giving a benzylic cation which would give the 3*H* isomer directly by proton loss. It



Scheme 9.

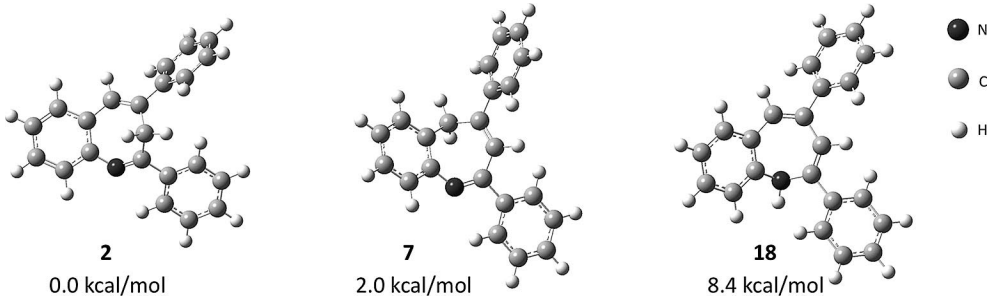


Figure 2. Relative energies of 3*H*-1-benzazepine **2**, 5*H*-1-benzazepine **7**, 1*H*-1-benzazepine **18** calculated at B3LYP/6-31G(d).

should be added that 2-substituted 5*H*-1-benzazepines are known to rearrange to give the more stable 3*H*-1-benzazepines.[2b]

NMR Spectroscopic Studies of the Benzazepines

Characterization of the benzazepines was initially hampered by anomalies in their ^{1}H NMR spectra. The two allylic protons at C3 were observed as a broad singlet in $CDCl_3$ at room temperature in most of the benzazepines shown in Schemes 1 and 4, with two exceptions. Since the azepine ring is non-planar, one would expect the two protons to be non-equivalent and possibly give separate resonances unless they exchange rapidly on the NMR time scale. We were able to slow down the exchange rate by lowering the temperature and thus observe two separate signals for each of the two allylic protons at C3 in all benzazepines. Alkyl substitution at C5 appreciably slows the conformational change. For example, two separate broad allylic proton resonances were observed at room temperature for **11b** and **11c** and they were confirmed by careful peak integration. The fact that all other benzazepines showed a single resonance for the allylic protons at room temperature means that the conformational change in these cases is relatively rapid, compared to benzazepines **11b** and **11c**. Of particular mention is one of the allylic proton resonances of **11b** buried underneath the methyl signal at δ = 2.36 ppm. This allylic signal was confirmed by integration as well as through a C–H correlation experiment. Upon lowering the temperature to –50 °C, the allylic resonances of **11b** sharpened and a geminal coupling of 12.0 Hz could be observed (Figure 3). The geminal coupling could not be observed in all the benzazepines because of exchange line broadening even at the limiting temperature of –64 °C, the freezing point of the $CDCl_3$ solvent.

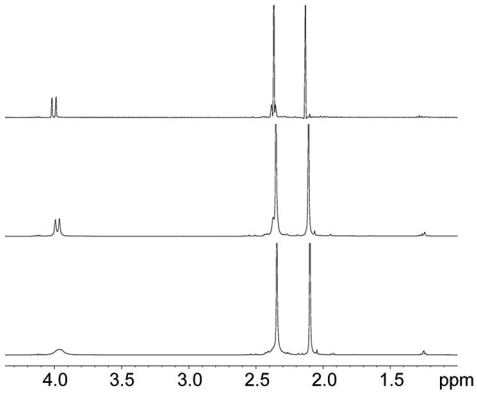


Figure 3. ^{1}H NMR spectra of 3*H*-benzazepine **11b** at 10 °C (bottom), –10 °C (middle) and –50 °C (top).

It is also important to compare and contrast the behavior of 3*H*-benzazepine **2** with 5*H*-benzazepine **7**. At room temperature, the allylic protons appear as single resonances at δ = 3.36 ppm and 3.55 ppm respectively for the 3*H*-benzazepine and 5*H*-benzazepine. Below –55 °C, the two allylic protons of the 3*H*-benzazepine split into two signals at δ = 2.21 ppm and 4.51 ppm, whereas the two allylic protons of the 5*H*-benzazepine split into two resonances at δ = 3.31 ppm and 3.87 ppm below –45 °C. The slight difference in the chemical shifts of the allylic protons in the 5*H*-isomer **7** vs. the large difference in the 3*H*-isomer **2** may be explained by the differing orientations of the aryl groups flanking the allylic protons.

Conclusions

This new synthesis gives facile access to the rarely studied 3*H*-1-benzazepine ring system. Calculations back-up a possible mechanism for the transformation, in which an intramolecular addition-elimination to an aromatic ring completes ring closure. The scope and limitations will be studied further, as will the factors which affect the equilibration of 1*H*-, 3*H*-, and 5*H*-1-benzazepines. Variable-temperature NMR spectroscopic studies indicate that the substitution pattern of the azepine ring affects its fluxional properties; a thorough study bolstered by molecular mechanics calculations will be forthcoming.

Experimental Section

General: Dypnone was obtained from Frinton Laboratories, Inc., Vineland, New Jersey, USA, www.frinton.com. ^{1}H and ^{13}C NMR spectra are referenced to tetramethylsilane. ^{19}F NMR spectra are referenced to CF_3CO_2H externally, set at –76.55 ppm.

Computational Methods: All calculations were carried out by B3LYP[14] alongside with the 6-31G(d)[15] basis with Gaussian 03.[16] Our B3LYP/6-31G(d) were successful in reproducing the values of bond lengths and bond angles available for benzazepine **11b** through X-ray analysis.[12] The combination of the B3LYP method and the 6-31G(d) basis set is know to reproduce geometries in a variety of experimental systems.[17] All compounds, except **16**–**17**, were characterized as minima or maxima on the corresponding potential energy surface (PES) by the frequency calculations. Structure **16**–**17** was found to be the third order saddle point. In addition to the analysis of the modes of the imaginary frequencies, transition stuctures were confirmed by tracing the intrinsic reaction coordinate (IRC).[18] All reported energies include unscaled ZPE corrections derived from frequency calculations. All structures were viewed with GaussView software.[19]

2,4-Diphenyl-5*H*-1-benzazepine (7): The crude reaction mixture containing a 1:12 mixture of benzazepines **7** and **2**, prepared on a 13.5-mmol scale as described previously,[3] was stirred with 1% EtOAc/hexanes (30 mL). The insoluble 3*H*-benzazepine isomer **2** was removed by suction filtration. The filtrate containing 5*H*-isomer **7** was stirred again with 1% EtOAc/hexanes (10 mL), and the supernatant was decanted, giving 832 mg of viscous amber oil which solidified upon standing. This was triturated with hexane (2 mL). The supernatant was pipetted off, and the solvent of this was removed by rotary evaporation. The resulting 343 mg of yellow oil contained mostly the 5*H*-isomer **7**. Radial chromatography (silica gel, 2 mm rotor, 5% EtOAc/hexane) gave 126 mg of a mixture of the two benzazepines, TLC R_f = 0.29. Radial chromatography (silica gel, 1 mm rotor, 50% toluene/hexane) gave 50 mg of 5*H*-benzazepine **7** (R_f = 0.30 in toluene; R_f of **2** = 0.39) as a yellow oil which solidified when placed in a freezer for several days, m.p. 96–

98 °C. Prolonged storage at low temperature in contact with glass causes isomerization to **2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (m, 2 H), 7.63 (dd, $^3J_{H,H}$ = 8.3,1.6 Hz, 2 H), 7.53 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.48 (m, 3 H), 7.38 (m, 4 H), 7.22 (tt, $^3J_{H,H}$ = 8.1,2.2 Hz, 2 H), 6.58 (s, 1 H), 3.55 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 149.0, 147.0, 140.3, 139.5, 131.0, 130.2, 128.8, 128.7, 128.5, 127.9, 127.2, 127.1, 127.0, 126.9, 126.3, 117.6, 36.4 ppm. HRMS calcd. for $C_{22}H_{17}N$ + H *m*/*z* 296.1434, found 296.1433.

3-Hydroxy-1-(4-methylphenyl)-3-[4-(trifluoromethyl)phenyl]butan-1-one (8a): To a solution of $TiCl_4$ (30 mL, 1.0 M in CH_2Cl_2, 30 mmol) under N_2 was added additional anhydrous CH_2Cl_2 (12 mL). The resulting solution was cooled to 5 °C and a solution of 4′-(trifluoromethyl)acetophenone (5.6 g, 30 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise, giving a yellow precipitate. A solution of the (trimethylsilyl)enol ether of 4′-methylacetophenone[6] (6.2 g, 30 mmol) in anhydrous CH_2Cl_2 (6 mL) was added dropwise, giving a dark red cloudy mixture. This was warmed to room temp. and held for 1 h. The crude mixture was poured into rapidly stirred ice water (70 mL). The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The three organic layers were combined and washed with 5% $NaHCO_3$ (2 × 20 mL), and once with brine (40 mL). The solution was dried with $MgSO_4$ and suction filtered through a short pad of silica gel. Rotary evaporation gave 8.4 g of viscous yellow liquid. Fractional recrystallization from hexane gave crops of **8a** as white powder, totaling 3.4 g (35% yield), m.p. 65–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dt, $^3J_{H,H}$ = 8.3,1.9 Hz, 2 H), 7.60 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.56 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.26 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 5.04 (s, 1 H), 3.78 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H), 3.34 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H), 2.42 (s, 3 H), 1.60 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 151.8, 145.1, 134.2, 129.5, 128.9 (q, $^3J_{H,H}$ = 33 Hz), 128.2, 125.3 (q, $^3J_{H,H}$ = 3.7 Hz), 124.9, 124.2 (q, $^3J_{H,H}$ = 272 Hz), 73.5, 48.2, 31.0, 21.7 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –63.1 ppm. HRMS calcd. for $C_{18}H_{17}F_3O_2$ + Na *m*/*z* 345.1073, found 345.1077.

3-Hydroxy-1-(4-methylphenyl)-3-phenylpentan-1-one (8b): The procedure as above using propiophenone gave 48% yield of aldol **8b** as white powder, m.p. 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.42 (m, 2 H), 7.29 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H), 7.23 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.18 (tt, $^3J_{H,H}$ = 7.4,1.2 Hz, 1 H), 4.93 (s, 1 H), 3.79 (d, $^3J_{H,H}$ = 17.3 Hz, 1 H), 3.26 (d, $^3J_{H,H}$ = 17.3 Hz, 1 H), 2.40 (s, 3 H), 1.84 (m, 2 H), 0.81 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 145.0, 144.7, 134.6, 129.4, 128.2, 128.1, 126.5, 125.0, 76.1, 47.1, 36.1, 21.7, 7.8 ppm. HRMS calcd. for $C_{18}H_{20}O_2$ + Na *m*/*z* 291.1356, found 291.1359.

2-(1-Hydroxycyclohexyl)-1-(4-methylphenyl)ethanone (8c): The procedure as above using cyclohexanone gave 60% yield of aldol **8c** as white needles, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.27 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 4.07 (s, 1 H), 3.09 (s, 2 H), 2.42 (s, 3 H), 1.73 (m, 4 H), 1.61 (m, 1 H), 1.45 (m, 4 H), 1.28 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 144.5, 135.1, 129.4, 128.3, 71.0, 47.4, 37.8, 25.8, 22.0, 22.7 ppm. HRMS calcd. for $C_{15}H_{20}O_2$ + Na *m*/*z* 255.1356, found 255.1360.

3-Hydroxy-3-methyl-1-(4-methylphenyl)butan-1-one (8d): The procedure as above using acetone gave 63% crude yield of aldol **8d**, which was carried through to the next step without purification.

3-Hydroxy-2-methyl-3-(4-methylphenyl)-1-phenylbutan-1-one (8e): The procedure as above using the (trimethylsilyl)enol ether of propiophenone, and 4′-methylacetophenone gave 48% yield of aldol **8e** as white powder, m.p. 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.42 (m, 2 H), 7.29 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H), 7.23 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.18 (tt, $^3J_{H,H}$ = 7.4,1.2 Hz, 1 H), 4.93 (s, 1 H), 3.79 (d, $^3J_{H,H}$ = 17.3 Hz, 1 H), 3.26 (d, $^3J_{H,H}$ = 17.3 Hz, 1 H), 2.40 (s, 3 H), 1.84 (m, 2 H), 0.81 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 145.0, 144.7, 134.6, 129.4, 128.2, 128.1, 126.5, 125.0, 76.1, 47.1, 36.1, 21.7, 7.8 ppm. HRMS calcd. for $C_{18}H_{20}O_2$ + Na *m*/*z* 291.1356, found 291.1361.

(2*E*)-1-(4-Methylphenyl)-3-[4-(trifluoromethyl)phenyl]but-2-en-1-one (9a): A solution of adol **8a** (1.30 g, 4.03 mmol), triethylamine (2.41 mL, 17.3 mmol), and 4-(dimethylamino)pyridine (54 mg, 0.44 mmol) in dry CH_2Cl_2 (6 mL) under N_2, was cooled to 0–5 °C. A solution of trifluoroacetic anyhydride (1.13 mL, 8.14 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. The resulting solution was warmed to room temp. and stirred for 22 h. The reaction solution was poured into rapidly stirred saturated Na_2CO_3 (30 mL) solution, and the resulting mixture was partitioned between H_2O (30 mL) and Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL). The two organic layers were combined, and dried with $MgSO_4$. Rotary evaporation gave 3.13 g of yellow-orange solid. Purification by radial chromatography (silica gel, 8 mm rotor, 5% EtOAc/hexane) gave 882 mg (72% yield) of enone **9a** as a yellow powder (R_f in 10% EtOAc/hexane = 0.44). Analytically pure samples were obtained by recrystallization from hexane, giving yellow crystalline powder, m.p. 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dt, $^3J_{H,H}$ = 8.2 & 1.7 Hz, 2 H), 7.69 (m, 4 H), 7.31 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.16 (q, $^3J_{H,H}$ = 1.3 Hz, 1 H), 2.58 (d, $^3J_{H,H}$ = 1.3 Hz, 3 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 152.5, 146.4, 143.8, 136.3, 130.8 (q, $^3J_{H,H}$ = 32.8 Hz), 129.4, 128.5, 126.8, 125.6 (q, $^3J_{H,H}$ = 3.7 Hz), 124.0 (q, $^3J_{H,H}$ = 272 Hz), 123.9, 21.7, 18.8 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –63.3 ppm. HRMS calcd. for $C_{18}H_{15}F_3O$ + H *m*/*z* 305.1148, found 305.1152.

(2*E*)-1-(4-Methylphenyl)-3-phenylpent-2-en-1-one (9b): The procedure as above, using aldol **8b**, gave 31% yield of enone **9b** as a yellow viscous oil after chromatography, which solidified upon standing, m.p. 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.53 (dd, $^3J_{H,H}$ = 7.6,2.0 Hz, 2 H), 7.40 (m, 3 H), 7.26 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.02 (s, 1 H), 3.05 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H), 2.41 (s, 3 H), 1.15 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 160.7, 143.3, 141.7, 136.7, 129.2, 128.9, 128.6, 128.5, 126.8, 122.1, 25.0, 21.6, 13.6 ppm. HRMS calcd. for $C_{18}H_{18}O$ + H *m*/*z* 251.1430, found 251.1434.

2-Cyclohexylidene-1-(4-methylphenyl)ethanone (9c): The procedure as above, using aldol **8c**, with a four-day reaction time and using 50% toluene/hexane as chromatography eluent, gave 52% yield of enone **9c** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.16 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 6.50 (s, 1 H), 2.68 (m, 2 H), 2.33 (s, 3 H), 2.23 (m, 2 H), 1.64 (m, 2 H), 1.56 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 162.1, 143.1, 136.7, 129.1, 128.5, 118.8, 38.4, 30.7, 28.9, 28.0, 26.3, 21.6 ppm. HRMS calcd. for $C_{15}H_{18}O$ + H *m*/*z* 215.1430, found 215.1427.

3-Methyl-1-(4-methylphenyl)but-2-en-1-one (9d):[20] Aldol **8d** in the crude reaction mixture spontaneously dehydrated to the enone **9d** upon standing for several days. Radial chromatography (silica gel, 15% EtOAc/hexane) gave enone **9d** as a colorless oil, TLC R_f in 20% EtOAc/hexane = 0.45. Overall yield from acetone and the (trimethylsilyl)enol ether of 4′-methylacetophenone = 35%.

2-Methyl-3-(4-methylphenyl)-1-phenylbut-3-en-1-one (10): The procedure as above, using aldol **8e**, and using 5% $NaHCO_3$ rather than saturated Na_2CO_3 for the work-up, and 25% CH_2Cl_2/hexane for

the chromatography, gave 41% yield of enone **10** as a colorless oil (TLC R_f in CH_2Cl_2 = 0.70) which solidified upon standing, m.p. 47–48 °C. The crude mixture also contained starting material which could be purified and recycled. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, $^3J_{H,H}$ = 7.2 & 1.4 Hz, 2 H), 7.52 (tt, $^3J_{H,H}$ = 7.4,1.4 Hz, 1 H), 7.40 (m, 4 H), 7.20 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H), 5.41 (s, 1 H), 5.03 (s, 1 H), 4.57 (q, $^3J_{H,H}$ = 6.8 Hz, 1 H), 2.39 (s, 3 H), 1.51 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 148.2, 137.8, 137.7, 136.4, 132.8, 129.3, 128.6, 128.5, 125.9, 114.1, 46.4, 21.1, 17.8 ppm. HRMS calcd. for $C_{18}H_{18}O$ + Na *m*/*z* 273.1250, found 273.1252.

2-(4-Methylphenyl)-4-[4-(trifluoromethyl)phenyl]-3*H*-1-benzazepine (11a): A solution of enone **9a** (523 mg, 1.72 mmol), 2-fluoroaniline (0.250 mL, 2.59 mmol) and *p*TsOH monohydrate (20 mg) in *o*-xylene (25 mL) was heated at reflux under N_2 for 19 h using Dean–Stark apparatus. The solution was cooled to room temp., and washed with 5% $NaHCO_3$ (25 mL). Drying over $MgSO_4$ and rotary evaporation gave 605 mg of yellow solid. Trituration with 5 mL 2% EtOAc/hexane and suction filtration gave 362 mg (56% yield) benzazepine **11a** as a beige solid. Analytically pure samples were obtained by dissolving in CH_2Cl_2 and passage of the solution over a short silica gel column, and then recrystallization from 15% EtOAc/hexane, giving light yellow crystalline powder, m.p. 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.66 (s, 4 H), 7.62 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.52 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.45 (td, $^3J_{H,H}$ = 7.6,1.5 Hz, 1 H), 7.27 (td, $^3J_{H,H}$ = 7.7,1.2 Hz, 1 H), 7.21 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.15 (s, 1 H), 3.42 (s, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 147.3, 143.4, 140.8, 135.1, 133.3, 130.6, 129.6 (q, $^3J_{H,H}$ = 32.7 Hz), 129.4, 129.0, 128.5, 128.1, 128.0, 127.5, 127.0, 125.8 (q, $^3J_{H,H}$ = 3.6 Hz), 124.1 (q, $^3J_{H,H}$ = 272 Hz), 124.0, 33.5, 21.4 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –63.1 ppm. HRMS calcd. for $C_{24}H_{18}F_3N$ + H *m*/*z*378.1464, found 378.1469.

5-Methyl-2-(4-methylphenyl)-4-phenyl-3*H*-1-benzazepine (11b): The procedure as above, using enone **9b** and 2 equiv. 2-fluoroaniline, and a six-hour reaction time, gave 53% yield of benzazepine **11b** as a yellow powder. Analytically pure samples and the sample for X-ray analysis were obtained by recrystallization from 25% EtOAc/hexane, giving large yellowish hexagonal crystals, m.p. 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 3 H), 7.52 (dd, $^3J_{H,H}$ = 8.0,1.5 Hz, 1 H), 7.33 (m, 4 H), 7.23 (m, 1 H), 7.14 (m, 4 H), 3.96 (broad s, 1 H), 2.36 (broad s, 1 H), 2.34 (s, 3 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 147.2, 142.3, 140.4, 134.9, 133.8, 133.4, 130.2, 129.1, 128.8, 128.4, 128.1, 127.3, 127.2, 126.9, 126.6, 123.5, 37.1, 21.4, 18.7 ppm. HRMS calcd. for $C_{24}H_{21}N$ + H *m*/*z* 324.1747, found 324.1750.

6-(4-Methylphenyl)-8,9,10,11-tetrahydro-7*H*-dibenzo[*b*,*d*]azepine (11c): The procedure was performed as above, using enone **9c** at a concentration of 0.04 M, and a reaction time of 22 h. Purification by radial chromatography (silica gel, 3% EtOAc/hexane) gave 54% yield of benzazepine **11c** as a yellow oil which solidified upon storage in a freezer. Analytically pure samples were obtained by recrystallization from hexane, giving yellowish pill-shaped solid, m.p. 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.62 (dd, $^3J_{H,H}$ = 7.9,1.5 Hz, 1 H), 7.51 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 7.32 (m, 3 H), 7.20 (dd, $^3J_{H,H}$ = 7.5,1.5 Hz, 1 H), 3.57 (broad s, 1 H), 2.87 (broad s, 1 H), 2.44 (s, 3 H), 2.28 (m, 4 H), 1.70 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 146.8, 140.6, 135.1, 133.5, 131.3, 129.9, 129.3, 128.2, 127.2, 126.1, 125.9, 123.5, 35.9, 31.5, 28.0, 22.9, 22.8, 21.4 ppm. HRMS calcd. for $C_{21}H_{21}N$ + H *m*/*z* 288.1747, found 288.1751.

2-Fluoro-*N*-[(1*E*,*Z*)-(2*E*)-2-methyl-3-(4-methylphenyl)-1-phenylbut-2-en-1-ylidene]aniline (12): A solution of enone **10** (162 mg, 0.647 mmol), 2-fluoroaniline (0.126 mL, 1.31 mmol) and *p*TsOH (8 mg) in *o*-xylene (15 mL) was heated for 20 h under N_2 in Dean–Stark apparatus. After cooling, the solution was washed with 5% $NaHCO_3$ (15 mL) and dried with $MgSO_4$. Rotary evaporation gave 199 mg of yellow viscous oil, which showed many components by TLC with 50% CH_2Cl_2/hexane. Radial chromatography (silica gel, 1 mm rotor, 25% CH_2Cl_2/hexane) gave 65 mg (29% yield) imine **12** as a yellow oil, TLC R_f in 50% CH_2Cl_2/hexane = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2 H), 7.49 (m, 3 H), 7.09 (m, 5 H), 6.94 (m, 1 H), 6.86 (m, 2 H), 2.32 (s, 3 H), 1.81 (s, 3 H), 1.60 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 152.9 (d, $^3J_{H,H}$ = 247 Hz), 139.5 (d, $^3J_{H,H}$ = 12.7 Hz), 139.2, 137.0, 136.5, 131.2, 129.0, 128.7, 128.5, 128.1, 127.6, 124.6 (d, $^3J_{H,H}$ = 7.4 Hz), 123.7 (d, $^3J_{H,H}$ = 3.8 Hz), 121.6 (d, $^3J_{H,H}$ = 2.3 Hz), 115.8 (d, $^3J_{H,H}$ = 20.0 Hz), 23.4, 21.2, 19.0 (d, $^3J_{H,H}$ = 3.0 Hz) ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –125.6 and –126.3 ppm, 6:1 area ratio, respectively. HRMS calcd. for $C_{24}H_{22}FN$ + H *m*/*z* 344.1809, found 344.1813. Presence of a 1:6 isomeric mixture is indicated by the ^{19}F spectrum, and also by the ^{1}H NMR spectrum. The latter showed three small singlets at δ = 2.26, 1.94, and 1.91 ppm; these are attributable to the methyl groups of the minor isomer. The area all of these together was 1/6 that of the three singlets at δ = 2.32, 1.81, and 1.60 ppm, which are the methyl groups of the major isomer. The ^{13}C spectrum showed a minor set of resonances accompanying all the peaks listed above.

2-Chloro-*N*-[(1*E*,*Z*)-(2*E*)-1,3-diphenylbut-2-en-1-ylidene]aniline (13): A solution of dypnone (1.00 g, 4.50 mmol), 2-chloroaniline (0.492 mL, 4.68 mmol) and *p*TsOH (46 mg) in toluene (57 mL) was heated at reflux under N_2 in Dean–Stark apparatus for 16 h. After cooling, the mixture was washed with 25 mL of 5% $NaHCO_3$ and dried with $MgSO_4$. Rotary evaporation gave 1.12 g of crude product, which showed only imine **13** and dypnone by ^{1}H NMR analysis. Radial chromatography (silica gel, 4 mm rotor, 75% toluene/hexane) gave 239 mg (16% yield) of imine **13** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (dd, $^3J_{H,H}$ = 8.4,1.4 Hz, 2 H), 7.39 (m, 3 H), 7.29 (dd, $^3J_{H,H}$ = 8.1,1.4 Hz, 1 H), 7.20 (m, 5 H), 7.10 (td, $^3J_{H,H}$ = 7.6,1.4 Hz, 1 H), 6.90 (td, $^3J_{H,H}$ = 7.7,1.5 Hz, 1 H), 6.81 (dd, $^3J_{H,H}$ = 7.8,1.3 Hz, 1 H), 6.28 (q, $^3J_{H,H}$ = 1.2 Hz, 1 H), 1.75 (d, $^3J_{H,H}$ = 1.2 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.6, 148.7, 142.8, 141.5, 138.4, 131.1, 129.8, 128.7, 128.6, 128.4, 128.1, 127.0, 125.9, 124.6, 124.5, 122.5, 121.2, 19.0 ppm. HRMS calcd. for $C_{22}H_{18}ClN$ + H *m*/*z* 332.1201, found 332.1196. Presence of a 1:11 isomeric mixture is indicated by peaks in the ^{1}H spectrum at δ = 6.05 ppm and 2.02 ppm; the former is attributable to the vinylic proton, and the latter to the methyl group, of the minor isomer. These two peaks individually had areas 1/11 that of the corresponding major-isomer peaks, the vinylic-proton quartet at δ = 6.28 ppm and the methyl-group doublet at δ = 1.75 ppm.

CCDC-756838 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also footnote on the first page of this article): Proton and carbon NMR spectra for all new compounds; details on calculations including Cartesian coordinates absolute energies, ZPE, imaginary frequencies; additional crystallographic details including tables of structural data.

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