Synthesis of Aryl-Substituted Piperidines by Superacid Activation of Piperidones

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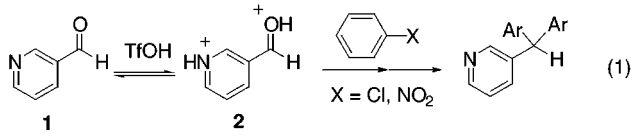
Diarylpiperidines (**8**−**12**) may be prepared in good to excellent yields (80−99%) by the reaction of piperidones (**3d**−**h**) with benzene and the Bronsted superacid, trifluoromethanesulfonic acid (CF_3SO_3H, TfOH). Tropinone (**6**) and quinuclidone (**7**) also react in good yields with benzene in TfOH to give the condensation products (**13** and **14**). Ketal and acetal derivatives also give condensation products (**8** and **24**) upon reaction with C_6H_6 in TfOH. The conversion of **3g** to **11** is sensitive to both acid quantity and acid strength; a mechanism is proposed for the conversion that invokes dicationic intermediates.

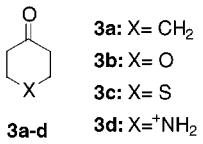
Introduction

The concept of superelectrophilic activation was first advanced by Olah in order to explain the reactivities of some electrophiles in superacid solution.[1] Superelectrophilic activation may occur when a cationic electrophile reacts with a Bronsted or Lewis acid to give a dicationic, superelectrophile. Superelectrophilic activation has been proposed in the Friedel−Crafts-type reactions of 1,2-dicarbonyl groups,[2] aldehydes,[3] nitriles,[4] and other systems.[5] We recently reported our studies of the trifluoromethanesulfonic acid (CF_3SO_3H, TfOH)-catalyzed condensation of 3-pyridinecarboxaldehyde (**1**) with deactivated aromatic compounds (eq 1) and the observation of dication **2** by low-temperature NMR.[6a] The results with **1** provided a demonstration of the reactivity of dicationic electrophiles and suggested that protonation of a strong, adjacent base site can activate an electrophilic functional group, such as a carboxonium ion.[6b]

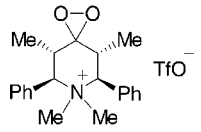


1 **2**

Seto and co-workers recently described the electrostatic field effects related to the nucleophilic attack on ketones **3a**−**d**.[7] Among the series, they found that the piperidone ring system **3d** is the most reactive toward nucleophilic attack by H_2O or thiols. In a similar respect, Yang and co-workers exploited the field effects in 4-oxopiperidinium salts in their studies of electrophilic dioxirane epoxidizing agents such as **4**.[8] These results suggested that piperidones might generate reactive dicationic electrophiles by diprotonation in superacidic solution.



3a-d



4

If reactive electrophiles can be generated from piperidones, then it should be possible to synthesize aryl-substituted piperidines by Friedel−Crafts chemistry. Piperidine compounds possess a variety of biological activities.[9] The aryl-substituted piperidines have been of particular interest because of their strong interaction with monoamine receptors associated with the central nervous system.[10] There have been some reports of the preparation of aryl-substituted piperidines from piperidones in $AlCl_3$−benzene solution,[11] and several reports have appeared in which intramolecular electrophilic aromatic substitution involving piperidones was accomplished with strong Bronsted acids.[12] In this paper, we describe the trifluoromethanesulfonic acid-catalyzed

(1) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 2, 767.
(2) (a) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *Synth. Lett.* **1998**, 918. (b) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481. (c) Yamazaki, T.; Saito, S.-i.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1995**, *36*, 5749.
(3) (a) Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211. (b) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081.
(4) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037.
(5) (a) Olah, G. A.; Klumpp, D. A.; Neyer, G.; Wang, Q. *Synthesis* **1996**, 321. (b) Klumpp, D. A.; Baek, D. N.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1997**, *62*, 6666. (c) Olah, G. A.; Wang, Q.; Neyer, G. *Synthesis* **1994**, 276. (d) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.*. **1994**, *116*, 2312. (e) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611.
(6) (a) Klumpp, D. A.; Lau, S., in press. (b) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364.
(7) Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285.
(8) Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem.* **1998**, *63*, 8952.
(9) (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine*; Elsevier: New York, 1991. (b) Numuta, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chapter 6, pp 193−315.
(10) (a) Giringauz, A. *Medicinal Chemistry*; Wiley-VHC: New York, 1997; pp 169−174. (b) Smith, M. P.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 9072. (c) Russ, H.; Pindur, U.; Przunutek, H. *J. Neural Transm.* **1986**, *65*(3−4), 157. (d) Neuser, D.; Stasch, J. P.; Witteller, M.; Kuhn, W.; Gerlach, M.; Jutzi, P.; Przuntek, H. *Eur. J. Pharmacol.* **1983**, *87*, 315. (e) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *Tetrahedron Lett.* **1999**, *40*, 403.
(11) (a) *Chem. Abstr.* **1973**, *78*, 124458. (b) German Patents: 2139084, 1936452. (c) Schaefer, H.; Hackmack, G.; Eistetter, K.; Krueger, U.; Menge, H. G.; Klosa, J. *Arzneim.-Forsch.* **1984**, *34*, 233.
(12) Takeda, M.; May, E. L. *J. Med. Chem.* **1970**, *13*, 1223.

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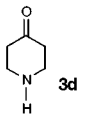
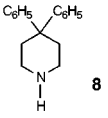
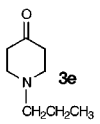
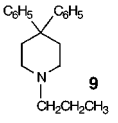
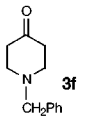
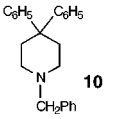
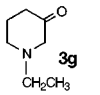
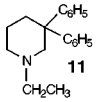
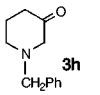
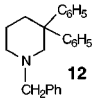
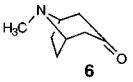
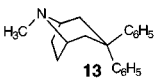
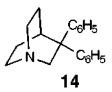
Table 1. Results from the Reactions of Piperidones 3d−h and Heterocycles 6 and 7 with Benzene in CF_3SO_3H

STARTING MATERIAL[a]	PRODUCT	YIELD
 **3d**	 **8**	99%
 **3e**	 **9**	99%
 **3f**	 **10**	99%
 **3g**	 **11**	80%
 **3h**	 **12**	90%
 **6**	 **13**	85%
 **7**	 **14**	71%

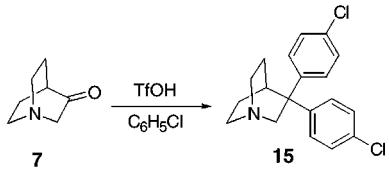
[a] **3d**, **3g**, and **7** were reacted as the hydrated hydrochloride salt.

condensations of piperidones and related systems with aromatic compounds to give diarylpiperidines. We also propose a mechanism in which reactive dications are generated.

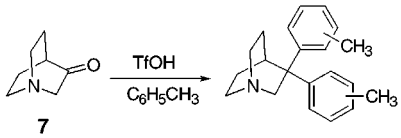
Results and Discussion

When piperidones **3d−h** are reacted with C_6H_6 in TfOH,[13] the condensation products **8−12** are formed in good to excellent yields (Table 1). In addition to the piperidones, the bicyclic systems of tropinone **6** and quinuclidone **7** also condense with C_6H_6 in TfOH to give products **13** and **14**, respectively. Ketone **7** reacts with substituted arenes such as chlorobenzene and alkylbenzenes. In the case of chlorobenzene, the condensation occurs regioselectively at the para position (eq 2), while in the case of toluene, the condensation gives the mixture of regioisomers (eq 3). Ketone **7** was also reacted with nitrobenzene and TfOH at 80 °C, but no condensation products were observed.

The condensation reaction has been found to be sensitive to both acid strength and acid quantity. Triflic acid

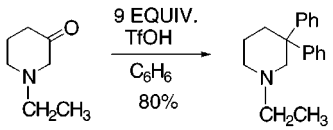


7 **15** (2)

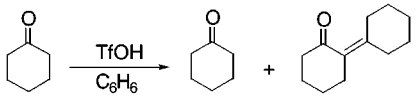


7 (3)

is up to 100 times stronger acid than H_2SO_4,[14] and when **3g** is reacted with C_6H_6 in H_2SO_4, no condensation reaction is seen. When **3g** is reacted with C_6H_6 and either 1.0 or 3.0 equiv of TfOH, complex product mixtures are produced. However, reaction of **3g** with C_6H_6 and 9.0 equiv of TfOH gives **11** as the exclusive product in 80% yield (eq 4). Cyclohexanone **3a** was also reacted with benzene in excess TfOH (30 equiv). No products are detected from reaction with benzene, although a small amount of the aldol condensation product can be detected (eq 5).



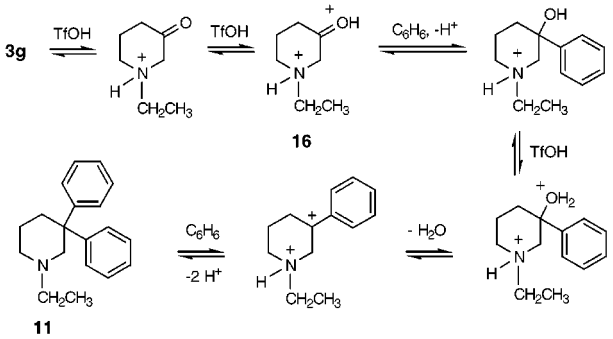
3g **11** (4)



3a (5)

A mechanism for the conversion of **3g** to **11** is proposed in Scheme 1. In superacidic TfOH, an equilibrium is

Scheme 1



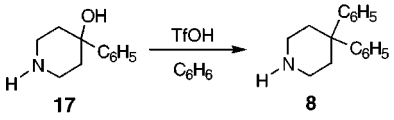
established between protonated intermediates. Given the dependence of the condensation reaction on acid quantity and acid strength, this suggests that the dication **16** is generated in the superacid. Intermediate **16** is sufficiently electrophilic to react with benzene leading to the condensation product **11**.[15] Under less acidic conditions, **16** is not formed in high enough concentration for the condensation reaction to occur at a significant rate and

(13) (a) For a review of TfOH chemistry, see: Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15. (b) TfOH may be quantitatively recycled; for a procedure, see: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.

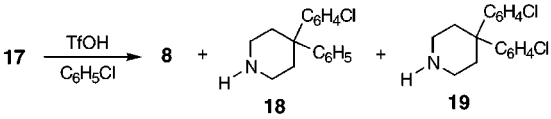
(14) Olah, G. A., Prakash, G. K. S., Sommer, J. In *Superacids*; Wiley: New York, 1985.

(15) Shudo, K.; Ohwada, T. In *Stable Carbocation Chemistry*; Prakash, G. K. S., Schleyer, P. v. R., Eds.; Wiley: New York, 1997; pp 525−548.

other reactions take place. Support for the proposed mechanism was obtained from reaction of the substituted piperidine **17** with C_6H_6 in TfOH (eq 6). In accord with the proposed mechanism, **17** gives the expected product (**8**) in good yield. When **17** was reacted with TfOH and chlorobenzene, compounds **8**, **18**, and **19** are the only major products (eq 7; formed in a ratio of 1.0:9.3:12.2, respectively). Similarly, compound **8** reacts with TfOH and chlorobenzene to give unreacted **8** and products **18** and **19** (ratio: 1.0:9.0:9.9). Compound **19** must be produced from the loss of the phenyl group(s). This suggests that the condensation of piperidones occurs with at least one reversible electrophilic aromatic substitution step.

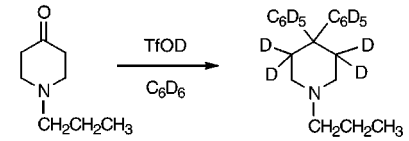


(6)

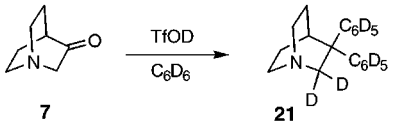


(7)

In addition to the reaction steps described in Scheme 1, the piperidone systems also undergo rapid, acid-catalyzed keto−enol tautomerizations.[16] Compounds **3e** and **7** were reacted with C_6D_6 in deuterated triflic acid, TfOD (eqs 8 and 9). Both condensation reactions were accompanied by nearly complete incorporation of deuterium at the α-positions to give products **20** and **21** (deuterium is not incorporated at the bridgehead position of product **21**). Moreover when **3e** is dissolved in TfOD without C_6D_6, incorporation of deuterium in the α-positions occurs quantitatively.



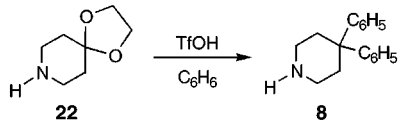
(8)



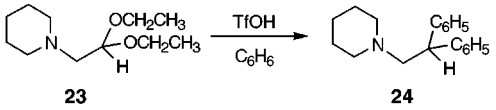
(9)

In addition to the condensations involving piperidones, tropinone, and quinuclidone, related ketal and acetal compounds react with C_6H_6 in TfOH. The ketal derivative of 4-piperidone (**22**) reacts with C_6H_6 in TfOH to give the condensation product **8** as the major product in about 50% yield (eq 10), while the acetal **23** gives the condensation product **24** in 75% yield (eq 11). The acetal and ketal groups are both cleaved in the superacid to yield electrophiles capable of reacting with C_6H_6. If an analogy is made with the condensations involving piperidones, these results suggest that dicationic carboxonium ions are involved in the formation of **8** and **24**.[17]

The condensations of the nitrogen heterocycles **3d**−**h**, **6**, and **7** with arenes are examples of hydroxyalkylation



(10)



(11)

reactions.[18] This well-known condensation reaction of aldehydes or ketones generally occurs only with activated arenes such as phenols or alkylbenzenes. Although cyclohexanone (**3a**) is extensively protonated in TfOH,[14] it does not react with benzene in a hydroxyalkylation reaction in TfOH. Heterocycles **3d**−**h**, **6**, and **7** are considerably more reactive than **3a** as electrophiles in TfOH. We propose that the origin of this enhanced reactivity is in the base site located at the nitrogen and that the protonated nitrogen activates the electrophilic carboxonium group. This activation may arise from inductive effects or by through-space electrostatic effects. In accord with Olah's concept of superelectrophilic aciv ation, this further illustrates the reactivity of dicationic electrophilies.

Conclusion

Diarylpiperidones are compounds that have been of interest as drugs in the treatment of various neurological disorders. We have found the diarylpiperidines are formed in good to excellent yields by the reaction of piperidones with arenes in trifluoromethanesulfonic acid (CF_3SO_3H, TfOH). We propose that the condensation reactions occur through reactive dicationic intermediates.

Experimental Section

Piperidones **3d**−**k** and compounds **6**, **7**, **16**, **22**, and **23** were purchased from Aldrich and used as received. Trifluoromethanesulfonic acid was purchased from 3M Co. and distilled under a dry, inert atmosphere immediately prior to its use. Benzene was dried with sodium prior to use. High-resolution mass spectra were recorded at the Mass Spectrometry Facility at the University of California, Riverside.

General Procedure for the Preparation of Diarylpiperidines. A 0.2 g portion of the piperidone (or related compounds **6**, **7**, **22**, and **23**) was dissolved or suspended in 2 mL of dry C_6H_6, and 2 mL of triflic acid was added.[19] The solution was stirred at room temperature for at least 3 h, after which the mixture was poured over several grams of ice. The aqueous solution was then made basic by addition of NaOH, and the products were extracted into $CHCl_3$. The organic solution was then washed with H_2O and brine, dried with $MgSO_4$, and concentrated in vacuo.

4,4-Diphenylpiperidine (8): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 2.52 (t, J = 3.9 Hz, 4H), 3.08 (t, J = 4.5, 4H), 7.18−7.30 (m, 6 H), 7.36 (m, 4 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 35.0, 42.3, 44.4, 126.3, 126.8, 128.3, 128.7; EI MS 237 (M^+); HRMS calcd for $C_{17}H_{19}N$ 237.1518, found 237.1519.

4,4-Diphenyl-*N*-propylpiperidine (9): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 0.96 (t, J = 7.2 Hz, 3H), 1.60 (m, 2H),

(16) Rappoport, Z. *The Chemistry of Enols*; Wiley: New York, 1990.
(17) Fukuzawa, S.; Tsuchimoto, T.; Hiyama, T. *J. Org. Chem.* **1997**, *62*, 151.
(18) Hofmann, J. E.; Schriesheim, A. In *Friedel−Crafts and Related Reaction*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol 2, pp 597−640.
(19) When the piperidone hydrochloride salts are reacted in TfOH, a significant amount of gas pressure is generated (presumably HCl gas). These reactions were done in a flask fitted with an outlet for gas pressure.

2.31 (m, 2H), 2.52−2.68 (broad s, 8 H), 7.18−7.25 (m, 4 H), 7.34−7.37 (m, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 12.0, 20.2, 36.2, 44.7, 50.6, 60.1, 125.6, 127.2, 128.2, 128.3; EI MS 279 (M^+); HRMS calcd for $C_{20}H_{25}N$ 279.1987, found 279.1989.

4,4-Diphenyl-*N*-benzylpiperidine (10): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 2.42−2.56 (m, 8 H), 3.40 (s, 2H), 7.10−7.16 (m, 4 H), 7.23−7.34 (m, 11H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 36.2, 44.7, 50.7, 63.3, 125.6, 127.0, 127.2, 128.2, 128.3, 128.3, 129.2, 138.7; EI MS 327 (M^+); HRMS calcd for $C_{24}H_{25}N$ 327.1987, found 327.1985.

3,3-Diphenyl-*N*-ethylpiperidine (11): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.23 (t, J = 7.5 Hz, 3H), 1.62 (m, 2H), 2.35 (m, 2H), 2.47−2.58 (m, 4H), 2.94 (s, 2H), 7.16−7.22 (m, 2H), 7.28−7.38 (m, 4H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 11.8, 22.4, 35.5, 46.3, 52.6, 54.3, 62.5, 125.5, 127.6, 127.9; EI MS 265 (M^+); HRMS calcd for $C_{19}H_{23}N$ 265.1831, found 265.1818.

3,3-Diphenyl-*N*-benzylpiperidine (12): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.68 (m, 2H), 2.40 (m, 2H), 2.58 (m, 2H), 3.00 (m, 2H), 3.64 (s, 2H), 7.20−7.28 (m, 2H), 7.33−7.38 (m, 8H), 7.43−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 22.3, 35.4, 46.6, 54.2, 63.2, 63.5, 125.6, 127.0, 127.8, 127.9, 128.1, 129.3, 138.6; EI MS 327 (M^+); HRMS calcd for $C_{24}H_{25}N$ 327.1987, found 327.1987.

3,3-Diphenyl-*N*-methyl-8-azabicyclo[3.2.1]octane (13): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.48 (m, 2H), 1.82 (m, 2H), 2.42 (s, 3H), 2.61 (m, 2H), 3.07 (m, 2H), 3.39 (m, 2H), 7.40−7.14 (m, 2H), 7.21−7.26 (m, 4H), 7.30−7.41 (m, 2H), 7.66−7.69 (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 24.2, 39.0, 39.3, 42.2, 61.0, 124.6, 125.0, 125.4, 125.5, 126.7, 127.8, 127.9, 128.2; EI MS 277 (M^+); HRMS calcd for $C_{20}H_{23}N$ 277.1831, found 277.1844.

3,3-Diphenyl-1-azabicyclo[2.2.2]octane (14): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.66 (m, 4H), 2.86 (m, 4H), 2.95 (m, 1H), 3.93 (s, 2H), 7.06−7.16 (m, 2H), 7.18−7.30 (m, 8 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 22.5, 28.5, 45.9, 46.7, 57.9, 125.7, 126.4, 128.5, 147.5; EI MS 263 (M^+); HRMS calcd for $C_{19}H_{21}N$ 263.1674, found 263.1675.

3,3-Bis(4-chlorophenyl)-1-azabicyclo[2.2.2]octane (15): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.56 (m, 2H), 1.65 (m, 2H), 2.78 (m, 4H), 2.87 (m, 1H), 3.84 (s, 2H), 7.04−7.09 (m, 2H), 7.19−7.30 (m, 6H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 23.2, 28.7, 47.0, 58.6, 125.4, 126.6, 128.3, 148.3; EI MS 331 (M^+); HRMS calcd for $C_{19}H_{19}Cl_2N$ 331.0895, found 331.0896.

***N*-Propyl-4,4-bis(pentadeuteriophenyl)-3,3,5,5-tetradeuteriopiperidine (19):** ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 0.86 (t, J = 7.2 Hz, 3H), 1.50 (m, 2H), 2.22 (m, 2H) 2.50 (s, 4H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 12.0, 20.2, 35.4, 50.5, 50.5, 60.9, 125.4, 127.1, 127.8, 128.1; EI MS 293 (M^+); HRMS calcd for $C_{20}H_{11}D_{14}N$ 293.2866, found 293.2855.

3,3-Bis(pentadeuteriophenyl)-2,2-dideutero-1-azabicyclo[2.2.2]octane (20): ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.56 (m, 2H), 1.65 (m, 2H), 1.97 (m, 2H), 2.43 (m, 1H), 2.79 (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 23.4, 25.6, 28.7, 39.6, 46.9, 125.0, 126.5, 127.7, 128.0; EI MS 275 (M^+); HRMS calcd for $C_{19}H_9D_{12}N$ 275.2427, found 275.2418.

***N*-(2,2-Diphenylethyl)piperidine (24):** ^{1}H NMR (300 MHz, $CHCl_3$) δ, ppm 1.36 (m, 2H), 1.48 (m, 4H), 2.39 (m, 4H), 2.95 (d, J = 7.2 Hz, 2H), 4.23 (t, J = 7.2 Hz, 1H), 7.13−7.26 (m, 10H); ^{13}C NMR (75 MHz, $CHCl_3$) δ, ppm 24.4, 25.9, 48.8, 54.9, 64.5, 126.1, 128.2, 128.3, 144.3; EI MS 98 (M − 167); HRMS(DCI/NH_3) calcd for $C_{19}H_{25}N$ (MH^+) 266.1909, found 266.1897.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **8**−**15**, **20**, **21**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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