Superacid promoted synthesis of 9,9’-spirobifluorenes and related aza- and diazaspirocycles.

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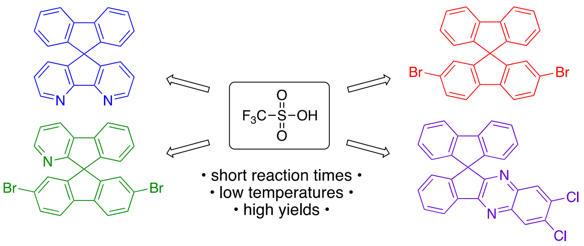
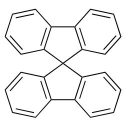
Supporting Information Placeholder



ABSTRACT: A variety of 9,9’-spirobifluorenes and related azaspirocycles and diazaspirocycles have been prepared in high yields by intramolecular Friedel-Crafts reaction using the Brønsted superacid, triflic acid (CF_3SO_3H). Compared to weaker Brønsted acids, the superacid consistently provides better yields along with reduced reaction times and it eliminates the need for heating. The superacid is particularly effective when dicationic electrophilic intermediates are generated in the conversions, for example with the diazaspirocycle syntheses.

Approximately 20-30% of electricity consumption is used for lighting and illumination within industrialized nations. As such, design improvements to light sources could have profound economic impacts and significant benefit to the environment. The pursuit of improved light sources has driven extensive research in the development of organic light emitting diodes (OLEDs) and related devices. In this regard, 9,9’-spirobifluorenes (i.e., **1**) have become an important target in organic synthesis, as this scaffold has found wide-spread use in organic-based electronic devices.[1] This includes numerous applications in the designs of OLEDs where the 9,9’-spirobifluorenes may serve as hole-transport, electron-transport, and emissive materials.[2] Similarly, spiro[cyclopenta[1,2-b:5,4-b']dipyridine-5,9'-fluorene] (**2**) and related azaspirocycles have useful electronic and optical properties due to the influence of the heteroatoms on the system.[3]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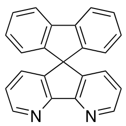

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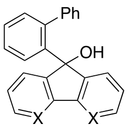


3a X=CH
3b X=N

With the widespread use of the 9,9’-spirobifluorenes in light-emitting devices (and other organic-based electronics), there has been an intense level of work towards the discovery of new spirocyclic compounds which have novel properties.[4] Likewise, there has been much effort devoted to the development of improved synthetic methods leading to these compounds.[5] The most common method of synthesis for the spirocycles has been the Friedel-Crafts reactions of the appropriate alcohol precursors (i.e., **3a,b**) in an acetic acid solution with catalytic HCl or H_2SO_4 – a synthetic method that dates to 1930.[6] This chemistry occurs through an intermediate or transition state resembling the 9-fluorenyl cation. Studies by Mills and others have shown that 9-fluorenyl cations possess significant anti-aromatic character.[7] As a high energy cationic species, we reasoned that superacidic media could be an outstanding reagent for generating the 9-fluorenyl cations and for promoting these valuable cyclodehydration reactions. Superacids are known for their good ionizing power and low coordinating counter-ions - conditions that should favor Friedel-Crafts reactions involving unstable or high energy carbocations.[8] Among the published cyclodehydrations leading to spirocyclic products, virtually all have used relatively weak Brønsted and Lewis acids. There has been one report in a recent patent where superacidic triflic acid was used to form a spirocycle (*vide infra*),[9] however beyond this example, there have been no other studies demonstrating the use of superacids to catalyze these types of conversions. In this Note, we describe the use of superacidic triflic acid (CF_3SO_3H) as a very effective acid promoter for intramolecular Friedel-Crafts reactions leading to spirocyclic structures. We show that the superacid provides the spirocycle products in higher yields with lower reactions temperatures and shorter reaction time than weaker acid catalysts. Mechanisms are proposed involving reactive fluorenyl cations and dications.

Table 1. Conversions of substrate **3b** to diazaspirocycle **2.**

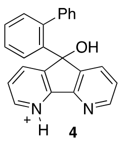
	acid	equiv.	time	temp.	yield **2**
1	AcOH, HCl	–	2 hr	reflux	60%[a,b]
2		–	3 hr	reflux	70%[a,c]
3	AcOH, H_2SO_4	–	24 hr	reflux	75%[a,d]
4		–	8 hr	reflux	81%[a,e]
5		–	8 hr	reflux	85%[a,f]
6		35	4 hr	25°C	0%
7	CF_3CO_2H	35	4 hr	80°C	0%
8	CF_3SO_3H	35	4 hr	25°C	97%[a]
9		35	1 hr	80°C	99%[a]
10		5.0	1 hr	25°C	84%[a]
11		5.0	1 hr	80°C	99%[a]
12		2.0	4 hr	25°C	28%[g]
13		1.0	4 hr	25°C	12%[g]
14		0.5	4 hr	25°C	5%[g]
15		0.5	24 hr	25°C	7%[g]

a. Isolated yield.
b. Ref. 10, 21 mmol **3b**, 0.2 L AcOH, 0.5 mL HCl.
c. Ref. 11, 100 mmol **3b**, 0.1 L AcOH, 5 mL HCl.
d. Ref. 12, 18.6 mmol **3b**, 0.5 L AcOH, 5 mL H_2SO_4.
e. Ref. 13, 0.1 mmol **3b**, 0.25 L AcOH, 3 mL H_2SO_4.
f. Ref. 14, 0.1 mmol **3b**, 0.22 L AcOH, 4 mL H_2SO_4.
g. Yield determined by NMR.

In order to test the efficiency of superacidic media for these Friedel-Crafts conversions, we examined the cyclization of alcohol **3b** to give the spiro[cyclopenta[1,2-b:5,4-b']dipyridine-5,9'-fluorene] **2** (Table 1). This diazaspirocycle has been described in several recent patents and manuscripts. It has been prepared in reasonably good yields (60-85%) from acetic acid-HCl and acetic acid-H_2SO_4.[10-15] Nevertheless, these methods require elevated temperature and/or extended reaction times for good conversion (entries 1-5). When superacidic CF_3SO_3H (triflic acid) is used in the conversion, a nearly quantitative conversion may be achieved at room temperature in less than 4 hours (entry 8). If the cyclodehydration is done at 80°C, the conversion is quantitative with a one hour reaction time (entry 9). With decreasing amounts of triflic acid, the conversion is still accomplished in high yield (entries 10 and 11), however with 2.0 equivalents of superacid (or less) the product yields decreases rapidly. Surprisingly, a low yield of spirocycle product **3** is also obtained with less than one equivalent of acid (entries 14 and 15). When the weaker acid CF_3CO_2H is used in the cyclodehydration (entry 7), no product was obtained. Similarly, the acetic acid-H_2SO_4 catalyst gives no product at low temperature and short reaction time (entry 6).

These results confirm that triflic acid is a superior acid catalyst for the intramolecular Friedel-Crafts reaction of compound **3b** to provide the diazaspirocycle **2**. Although triflic acid is considerably more expensive than acetic acid, HCl or H_2SO_4, a procedure has been reported for the quantitative recycling of spent CF_3SO_3H.[16] Moreover, the conversions done in acetic acid require a workup step involving the quenching of acetic acid (the solvent) with large amounts of NaOH. Thus, the triflic acid promoted chemistry may reduce waste from the synthesis of these spirocyclic compounds.

The utility of the superacid may be understood by considering the cationic intermediates involved in the conversion. Ionization of alcohol **3b** begins with protonation of the nitrogen base site to give cation **4**. Protonation of the second nitrogen seems unlikely – given the proximity of the two base sites. The intramolecular Friedel-Crafts reaction requires formation of reactive dicationic species, first the oxonium dication **5** and then the dication **6**.[17] It is suggested that the superacid more readily generates the dicationic intermediates – allowing the cyclodehydration to be accomplished with lower temperatures and shorter reaction times compared to the weaker Brønsted acid catalysts. When less than one equivalent of superacid is used in the conversion, a 5-7% yield of the spirocycle is obtained. Since protonation of the *N*-base site should be highly favored and the acid would be completely consumed to make cation **4**, how can ionization of the fluorenol group be explained? This may be the consequence of incomplete mixing of the reagents – when the superacid is added to the solution of **3b**, a locally high concentration of the acid is present and cyclization occurs. With further mixing, the protons settle into the strong base sites and cyclization no longer occurs.



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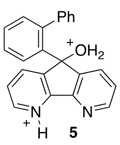

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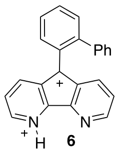

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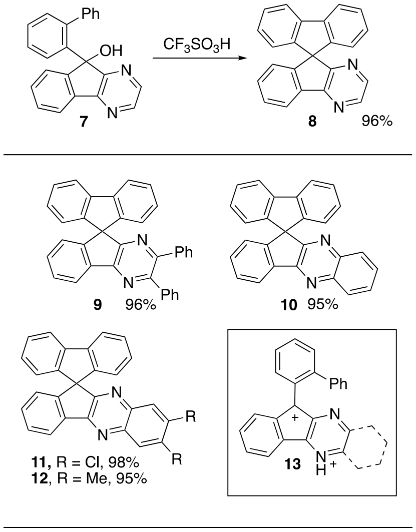
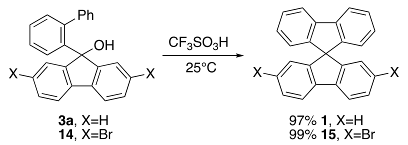
Scheme 1. Cyclizations of diazine systems.



The superacid promoted intramolecular Friedel-Crafts reaction is effective with other *N*-heterocyclic systems. A series of spirocyclic diazine compounds were prepared in excellent yields from the corresponding alcohols (Scheme 1). Thus, substrate **7** is reacted in triflic acid to provide the spirocycle **8** in nearly quantitative yield. NMR analysis shows essentially pure crude product from the reaction. As in the previous conversion, this product is obtained from a reaction at 25°C within 4 hours. The phenyl substituted derivative **9** is likewise prepared in good yield from the analogous cyclodehydration. The superacid also provides excellent yields of the ring-fused products **10-12**. These substances are prepared in three steps from ninhydrin. Condensation of ninhydrin with diaminobenzenes lead to the azafluorenones and subsequent reactions with 2-lithiobiphenyl provide the corresponding azafluorenols. The intramolecular Friedel-Crafts reaction with triflic acid then gives the ring-fused products **10-12**. Presumably, these cyclizations involve multiply-charged cation electrophiles, such as dication **13**.

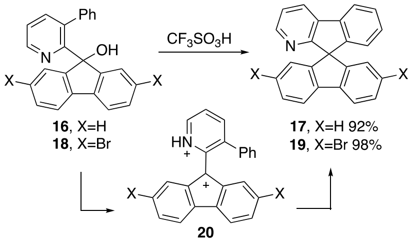
In each of the conversions above, multiply-charged diazafluorenyl ring systems undergo cyclization. The superacid is also effective with fluorenyl cation cyclizations. For example, 9,9'-spirobifluorene (**1**) is prepared in 97% yield at room



temperature from the fluorenol precursor (**3a**). The dibrominated system undergoes the Friedel-Crafts chemistry quantitatively to provide spirocycle **15** from the alcohol **14**. Compound **15** is an important building block for functionalized 9,9'-spirobifluorenes used in organoelectronics.[1-4,18] The superacid is again shown to be a superior reagent for this cyclodehydration, as the previous best conversion was described as an 89% yield of **15** from compound **14** in acetic acid-HCl at 140°C.[18d]

The superacid catalyst is also effective in reactions where cyclizations occur with a moderately deactivated aryl nucleophile and the 9-fluorenyl cation. For example, ionization of alcohols **16** and **18** generate the dicationic intermediates **20** (Scheme 2).

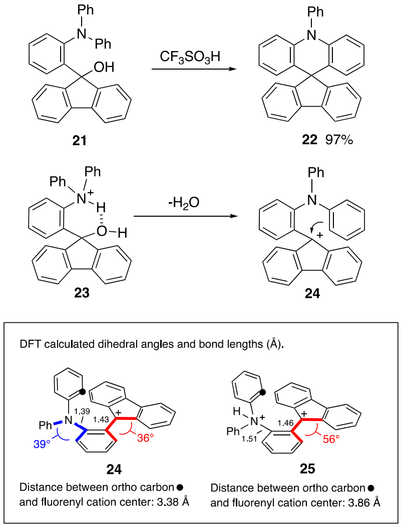
Scheme 2. Cyclizations to the aza-fluorene spirocycles.



The pyridinium ring likely reduces the nucleophilic reactivity of the phenyl group. Despite this effect, the cyclizations occur in high yield to provide the azaspirocycles (**17** and **19**) in excellent yields.

The aniline derivative **21** provides a good yield of the acridine spirocycle **22** (Scheme 3), a useful structure in organic electronics such as PhOLEDS[20] and TADF OLEDs.[21] Remarkably, a recent patent described a triflic acid-catalyzed conversion of **21** to **22** using a sub-stoichiometric amount (0.4 equivalents) of the superacid and providing spirocycle **22** in 91% yield.[9] With larger amounts of triflic acid, (35 equivalents), we were able to increase the yield to being nearly quantitative. Because the cyclodehydration eliminates water into the reaction media, this suggests a reaction largely catalyzed by hydronium triflate. Modelling studies indicate protonation of the aniline base-site occurs with strong hydrogen bonding to the fluorenol group (**23**).[21] This structure may facilitate ionization at the alcohol group to give the fluorenyl cation **24**. DFT computational modelling shows evidence of fluorenyl cation center stabilization by delocalization of the nitrogen lone pair in cation **24**. The structural parameters include a planar nitrogen center in **24**, dihedral angles of 39° and 36°, and short C-N and C-C bond distances – compared to the dicationic species (**25**). Interestingly, the distance between the fluorenyl cation center and the nearest ortho carbon is just 3.38 Å in the monocationic species **24** but increases to 3.86 Å in the dication **25**. With loss of conjugation to the nitrogen lone pair and electrostatic effects from the second positive charge, dication **25** adopts a more open structure with longer bonds and an increasing dihedral angle between the fluorenyl cation and the adjacent aryl ring. This suggests a preference for the monocation **24** in the cyclization chemistry. Moreover, this allows the cyclodehydation to be accomplished in good yield with a small amount of superacid catalyst.

Scheme 3. Cyclization to spirocycle **22**.



This conversion (**21** -> **22**) appears to be unique among the intramolecular Friedel-Crafts reactions. When a similar procedure was attempted with fluorenols **3a** and **3b** much lower yields of spirocycle products were obtained at low concentrations of superacid. As shown in Table 1, 0.5 equivalents of CF_3SO_3H only provides about 5% yield of the diazaspirocycle **2** from the corresponding alcohol **3b** (entry 14). Similarly, fluorenol **3a** provides 9,9'-spirobifluorene (**1**) in diminishing yield with lowering amounts of triflic acid. Whereas 35 equivalents of triflic acid gives a 97% yield of the cyclization product **1** and the same yield is obtained with 2.0 equivalents of acid, but the yield drops to 76% with 1.0 equivalents of acid and 22% yield with 0.5 equivalents of acid. Considering that these conversions are carried out at 25 °C and 4 hr reaction time, the results do suggest that good yields of spirocycles may be obtained with relatively small quantities of superacid. The exact amount of superacid depends on the specific system undergoing cyclodehydration and the relative stabilities of the fluorenyl cation intermediates.

In summary, we have found that triflic acid is an excellent acid catalyst or promoter for intramolecular Friedel-Crafts reactions leading to 9,9'-spirobifluorenes and related spirocycles. The superacid allows the cyclizations to be done at lower temperatures and with shorter reaction times compared to previously used acid systems. It is proposed that the superacid leads to cleaner formation of the reactive carbocation intermediates, some of which are dicationic.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and procedures; spectra for all unknown compounds; computational methods and results (PDF).

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Notes

The authors declare no competing interests.

ACKNOWLEDGMENT

The support of the NSF (award no. 1955584) is gratefully acknowledged. We also acknowledge the generous support from the NSF MRI program (award no. CHE 1726931) for the purchase of a high-resolution mass spectrometer and Northern Illinois University for the support of the Molecular Analysis Core Facility. We thank the reviewers for helpful comments.

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(21) For details regarding computations, see Supporting Information Section.