

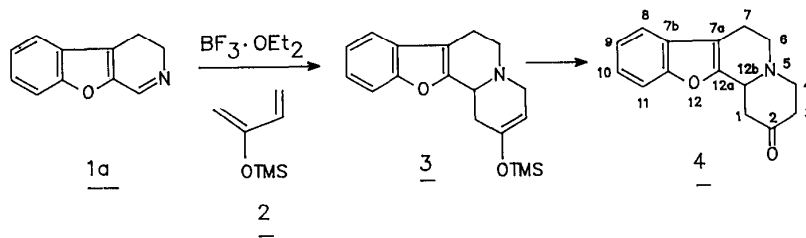
ENHANCED REACTIVITY OF IMINIUM IONS AS HETERODIENOPHILES
IN LEWIS ACID MEDIATED 4+2 CYCLOADDITION REACTIONS

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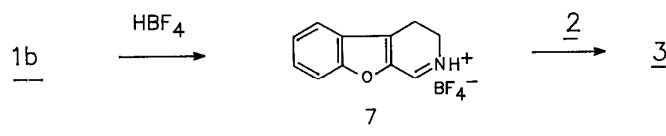
Summary: The use of a Lewis acid-proton acid combination was found to be highly effective for the activation of imines as heterodienophiles in Diels-Alder cycloaddition reactions.

The ability of an imine group to function as a heterodienophile in an apparent Diels-Alder cycloaddition reaction with a conjugated diene has been shown to possess a vast potential for the synthesis of a variety of nitrogen containing heterocycles.¹ However, not all imino compounds are effective dienophiles in 4+2 cycloaddition reactions unless exceptionally reactive dienes are employed. This unreactivity has been traditionally overcome by activation of the imine function by substitution with one or more electron withdrawing groups and/or the use of Lewis acid catalysis.^{2,3} In addition there have been several recent reports concerning the cycloaddition of Mannich generated iminium ions with conjugated dienes.⁴ We now wish to report our findings concerning the enhanced reactivity of iminium ions as heterodienophiles in the presence of Lewis acids.



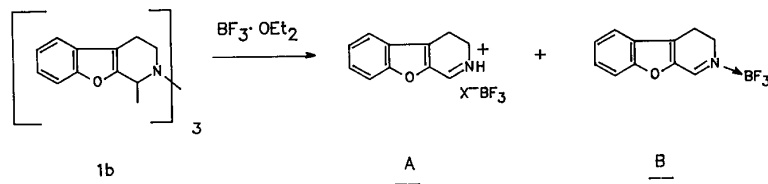
treated with trifluoroacetic acid in methylene chloride or chloroform to give the iminium trifluoroacetate 5. Subsequent addition of 1.0 equivalent of boron trifluoride etherate resulted in the quantitative production of the more reactive BF_3 mediated iminium species 6. ^1H NMR indicated that the nitrogen of imine 6 was protonated with the N-H broadened and in rapid exchange at ambient temperature; however, at -20°C a 9.0 Hz vicinal coupling between the imine N-H proton and the methine C-H was observed. Treatment of 6 with diene 2 led to a quantitative conversion to the desired enol silyl ether 3⁸. Iminium trifluoroacetate species 5 did not undergo cycloaddition in the presence of diene 2.

The reactive species is believed to be the protonated iminium ion 6 with the boron trifluoride associated with the trifluoroacetate counterion. This association should make iminium ion 6 more naked and hence more reactive. The BF_3 -counterion association is supported by ^{19}F NMR studies showing both an associated and non-associated trifluoroacetate species ^{7,9}. This hypothesis is further supported by the clean, quantitative conversion of the iminium tetrafluoroborate salt to the enol silyl ether 3 in the absence of a Lewis acid.



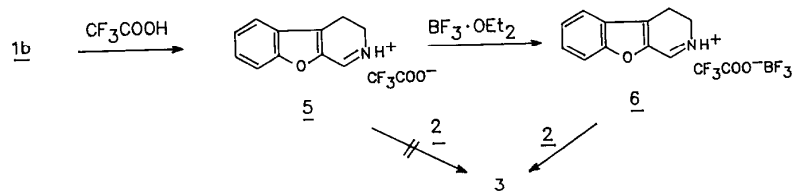
Procedure: To a stirred solution of imine trimer 1b (855 mg, 5.0 mmol) in 15 ml of dry dichloromethane at ambient temperature was added trifluoroacetic acid (385 μL , 5.0 mmol). The solution was stirred for 5 min and boron trifluoride etherate (615 μL , 5.0 mmol) was added. After 5 min the solution was treated with diene 2 (1.32 mL, 7.5 mmol) and stirred an additional 30 min at $22\text{--}24^\circ$. The reaction was quenched by washing with two portions of saturated sodium bicarbonate solution (30 mL each). The organic phase was separated, dried (Na_2SO_4), and concentrated to give enol silyl ether 3 as a yellow oil¹⁰. The oil 3 was dissolved in methanol (20 mL) and stirred over anhydrous sodium carbonate (0.5 g) at $22\text{--}24^\circ$ for 1 hr. The solution was filtered, concentrated, and partitioned between dichloromethane and water. The organic phase was dried (Na_2SO_4) and concentrated to give 1.10 g (91%) of ketone 4¹⁰ as a yellow oil which slowly crystallized on standing.

The Lewis acid catalyzed ($\text{BF}_3 \cdot \text{OEt}_2$ or ZnCl_2) cycloaddition of 3,4-dihydro-benzofuro[2,3-c]pyridine (1a)⁵ with 2-(trimethylsilyloxy)-1,3-butadiene (2) to give the silyl enol ether 3 was recently reported by Vacca as a general methodology for the synthesis of aryl[2,3-a]quinolizin-2-ones (4).⁶ This finding and our interest in the quinolizinone system has led us to further investigate this cycloaddition. We found



that treatment of benzofuropyridine trimer 1b with $\text{BF}_3 \cdot \text{OEt}_2$ gave rise to two distinct monomeric imine species, A (H-C=N , $\delta=8.9$) and B (H-C=N , $\delta=8.6$), of which only species A was converted to silyl enol ether 3 upon addition of diene 2. Furthermore, the relative amounts of imine species A and B produced were found to be dependent on the purity of both the reagents and the solvents used in the reaction. Species A and B were characterized by multinuclear NMR studies and the results are discussed below.

Species B was prepared quantitatively from trimer 1b by treatment with freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ in anhydrous methylene chloride and could be isolated as a solid. The ^{13}C NMR for imine B shows a 3-bond coupling ($J=3.5$ Hz) between the sp^2 imine carbon and the boron fluorines ($-\text{C}=\text{N}-\text{B}-\text{F}$). Furthermore ^{11}B and ^{19}F NMR show a $^{19}\text{F}-^{11}\text{B}$ splitting indicative of an almost symmetrical tetrahedral boron species. These facts imply a strong B-N interaction⁷. However, the ^1H NMR of reactive species A showed a broad, rapidly exchanging N-H signal indicating the presence of an adventitious proton source. An analogous iminium species was prepared as follows. Trimer 1b was first



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- Monomeric species 1a exists in equilibrium with the corresponding trimer 1b with the latter predominating under neutral or basic conditions.
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- Selected NMR data for B and 6. ^{19}F and ^{11}B spectra were obtained in CDCl_3 on a Bruker WM-250 referenced as follows: ^{19}F , C_6F_6 , $\delta_{\text{F}} = -163.0$ ppm; ^{11}B , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\delta_{\text{B}} = 0.0$ ppm. Negative chemical shifts are to higher field. B: $\text{N} \rightarrow \text{BF}_3$, $\delta_{\text{B}} = -0.45$ ppm, $\delta_{\text{F}} = -155.2$, $^1J_{\text{BF}} = 12$ Hz. 6: $\text{CF}_3\text{CO}_2^- \text{BF}_3$, $\delta_{\text{B}} = -0.54$ ppm, $\delta_{\text{F}} = -76.7$ ($-\text{CF}_3$), $\delta_{\text{F}} = -149.7$ (BF_3); excess free $\text{CF}_3\text{CO}_2\text{H}$, $\delta_{\text{F}} = -76.2$.
- Other acid/Lewis acid combinations were found to be less effective.
- Multinuclear NMR (^{13}C , ^{11}B , ^{19}F) and FT-IR studies with triethylammonium trifluoroacetate and boron trifluoride etherate show completely analogous results.
- NMR data for 3 and 4. Hydrogen and ^{13}C NMR experiments were run in CDCl_3 on Bruker WM-250 and AM-300 spectrometers. Assignments were made using homo- and hetero nuclear 2-D experiments (COSY-45, HETCOR). Fully ^1H coupled ^{13}C spectra were used to assign the quaternary carbons in 4. Since ^1H spectra consist primarily of overlapped multiplets the more informative ^{13}C data are reported.
 ^{13}C NMR 3: (CDCl_3 , $\delta_{\text{C}} = 77.0$ ppm) 0.33($\text{OSi}(\text{CH}_3)_3$), 21.0(C_7), 34.2(C_1), 51.2(C_6), 52.9(C_4), 55.9($\text{C}_{12\text{b}}$), 101.4(C_3), 111.0($\text{C}_{7\text{a}}$), 111.2(C_{11}), 118.8(C_8), 122.4(C_9), 123.4(C_{10}), 128.1($\text{C}_{7\text{a}}$), 148.1(C_2), 153.3($\text{C}_{12\text{a}}$), 154.9($\text{C}_{11\text{a}}$). 4: (CDCl_3 , $\delta_{\text{C}} = 77.0$ ppm) 20.9(C_7), 41.2(C_3), 43.7(C_1), 51.0(C_6), 53.6(C_4), 58.1 ($\text{C}_{12\text{b}}$), 111.0($\text{C}_{7\text{b}}$, C_{11}), 118.6(C_8), 122.3(C_9), 123.5(C_{10}), 127.5($\text{C}_{7\text{a}}$), 151.5 ($\text{C}_{12\text{a}}$), 154.4($\text{C}_{11\text{a}}$), 206.7(C_2).

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