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Tuning the reactivity and chemoselectivity of electron-poor pyrroles as dienophiles in cycloadditions with electron-rich dienes

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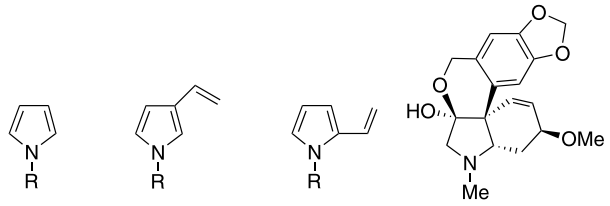
Abstract—Activation by Lewis acid catalysis and high pressure allows pyrrole derivatives to react with electron-rich dienes in normal electron demand [4+2] cycloadditions, provided that the aromatic ring is substituted by at least two electron-withdrawing groups. The dienophilic behavior of the heterocycle is expressed through the involvement of either the aromatic carbon–carbon double bond in an all-carbon process or the carbonyl moiety of the substituent in a heterocycloaddition reaction. In this regard, the nature of the heterocyclic substituents is shown to have a dramatic influence and to direct both the reactivity and the chemoselectivity of the cycloaddition.

1. Introduction

The Diels–Alder (DA) cycloaddition represents an efficient tool for the convergent and stereocontrolled synthesis of functionalized polycyclic systems.[1] The scope of the reaction is large and allows the synthesis of cyclohexene derivatives but also of a variety of heterocycles by swapping carbon atoms on the diene and/or dienophile with heteroatoms (O, N, S for instance; the so-called hetero-Diels–Alder reaction (HDA)).[2]

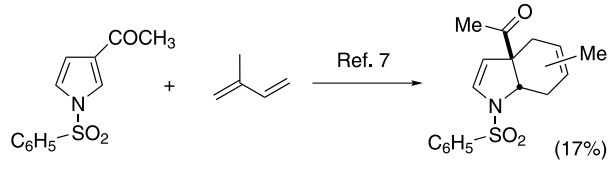
The use of five-membered aromatic heterocycles in these cycloadditions is almost as old as the reaction itself, and different possibilities have been described, depending on the substrate.[3] In this context, pyrrole **1** was soon considered as diene by involving either all four π-electrons of the heterocycle or only two of them, as in **2** and **3** (Fig. 1).[4]



1 **2** **3** **6**

Figure 1. Structures of pyrroles **1–3** and tazettine **6**.

In contrast, the literature mentions only a few reports on pyrrole derivatives acting as dienophiles in inverse electron-demand cycloaddition reactions.[5] Even scarcer are the cases relating to the involvement of this heteroaromatic cycle as dienophile in normal electron-demand [4+2]. To our knowledge, before our work,[6] the only example was published 15 years ago.[7] This behavior required the presence of two electron-withdrawing substituents on the N–C=C moiety of the aromatic ring. Thus, pyrrole **4**, bearing both an acetyl group on carbon 3 of the heterocycle and a benzenesulfonyl unit on position 1, reacted with isoprene to deliver compounds **5** as a 1:2 regioisomeric mixture (Scheme 1). Interestingly, these cycloadducts feature a quaternary carbon at the ring junction and are irreversibly dearomatized during the process. However, harsh conditions (195 °C, 72 h) had to be used and the isolated yield was low, thus forbidding the practical development of this approach and its use in the synthesis of products encompassing a five-membered nitrogen heterocycle (e.g., tazettine **6**). This result nevertheless pointed out the feasibility of such a reaction.



4 **5**

Scheme 1.

Keywords: Pyrrole; Diels–Alder reaction; Heterocycloaddition; Chemoselectivity; High pressure.
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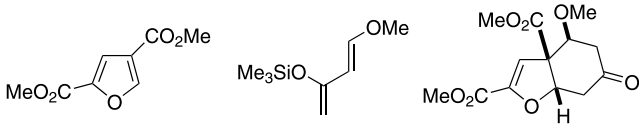
We recently reported that the analogous process involving the more reactive indole derivatives can be carried out in an efficient manner when activated by the combined action of a Lewis acid and high pressures.[8]

The more pronounced aromatic character of pyrrole led us to consider the activating effect of a third electron withdrawing substituent to generate a usable cycloaddition process. Thus, the known and easily accessible trisubstituted pyrrole **7**[9] was selected as the first substrate to study this dienophilic behavior. The choice of the 2,4-regioisomer was dictated by the nearly complete lack of reactivity of electron-poor five-membered heterocycles bearing an electron withdrawing group on carbon 2, thereby warranting a probable site selectivity on the heterocycle.[6,10] In addition the documented interaction between 2,4-biscarbomethoxy-furan **8** and Danishefsky's diene **9** was reported to involve the C4,C5 carbon–carbon double bond in a complete regioselective fashion, exclusively furnishing cycloadduct **10** after hydrolysis (Fig. 2).[11]



8 9 10

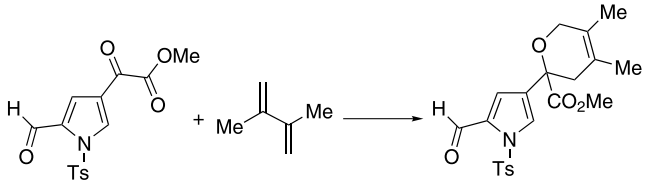
Figure 2. Structures of furan **8**, diene **9** and cycloadduct **10**.

2. Results and discussion

Reacting pyrrole **7** with excess 2,3-dimethylbuta-1,3-diene **11** at 100 °C for 72 h in the presence of zinc chloride (10% mol) led to an 85% consumption of the starting substrate. Purification of the crude residue furnished a material whose mass spectrometry indicated the presence of a 1:1 cycloadduct (21% isolated yield). Further analyses led to the identification of structure **12**, the result of an hetero Diels–Alder process between the 4-keto unit and the diene (Table 1, entry 1). Activation by either high pressure alone (entry 2), or a combination of high pressure and Lewis acid (entry 3) did not change the course of the reaction. Low conversion rates are believed to be the result of the competitive polymerization process which (i) slows the diffusion rate down and (ii) decreases the diene concentration.[12] As the resultant polymer also renders isolation difficult, attempts to solve these problems included diminishing the number of equivalents of diene. This led to a slightly better but still modest 28% isolated yield (entry 4).

The use of Danishefsky's diene **9** led to an analogous chemoselectivity, the 4-keto moiety proving once again to

Table 1. Reaction between pyrrole **7** and diene **11**

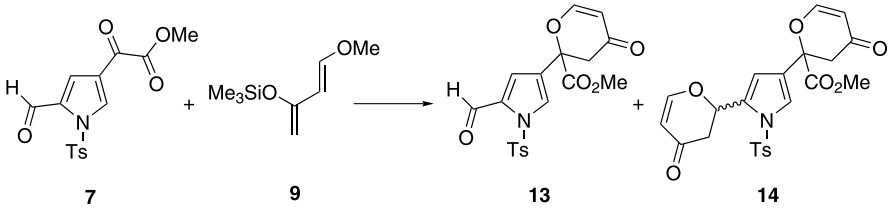


7 11 12

Entry	**11** (equiv)	*P* (GPa)	*T* (°C)	Cat.[a]	*t* (h)	Conv.[b] (%)	Yield (%)
1	12	10^{-4}	100	$ZnCl_2$	72	85	21
2	12	1.6	25	—	24	14	—[c]
3	12	1.6	25	$ZnCl_2$	24	36	—[c]
4	4	1.2	25	$ZnCl_2$	72	52	28

[a] 0.1 Catalysed (0.1 equiv) was used was used.
[b] Conversion.
[c] Not isolated.

Table 2. Cycloaddition between pyrrole **7** and diene **9**

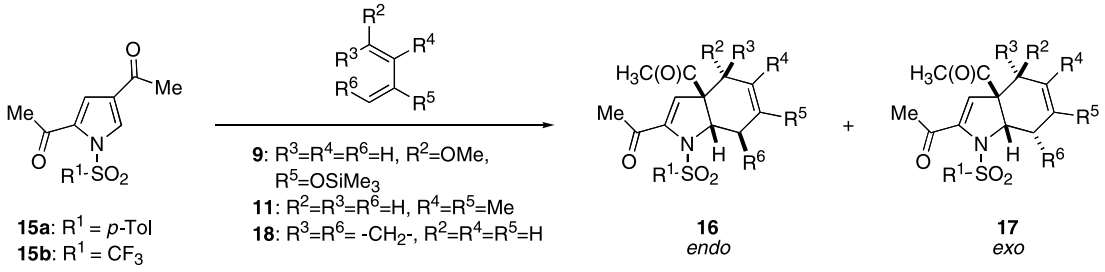


7 9 13 14

Entry	**7** (equiv)	*P* (GPa)	Cat.[a]	*T* (h)	Conv.[b] (%)	Ratio **13**:**14**	Yield (%)	
							13	**14**
1	1.5	10^{-4}	—	20	100	92:8	90	5
2	2	1.2	—	72	100	76:24	66	18
3	12	1.6	EuFOD	24	53	45:55	18	24

[a] 0.1 Catalysed (0.1 equiv) was used was used.
[b] Conversion.

Table 3. Cycloaddition between diacetylpyrroles **15** and dienes **9**, **11** and **18**



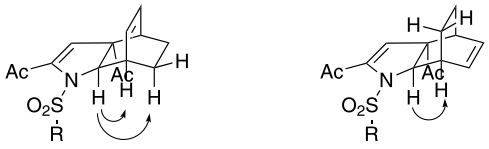
Entry	Dienophile	Diene (equiv)	*P* (GPa)	*T* (°C)	Cat.[a]	*t* (h)	Conv.(%)[b]	Product	*endo*/*exo*	Yield (%)
1	**15a**	**11** (12)	10^{-4}	130	$ZnCl_2$	168	38	**16a**	—	19
2	**15a**	**11** (12)	1.2	50	—	72	0	**16a**	—	—
3	**15a**	**11** (6)	1.2	50	$ZnCl_2$	72	47	**16a**	—	40
4	**15a**	**11** (6)	1.2	50	$ZnCl_2$	72	59	**16a**	—	48[c]
5	**15a**	**18** (6)	1.2	50	$ZnCl_2$	36	44	**16b/17b**	7/93	31
6	**15a**	**9** (6)	1.6	50	EuFOD	72	23	**16c/17c**	—	0[d]
7	**15b**	**11** (12)	10^{-4}	130	$ZnCl_2$	24	100	**16d**	—	0[e]
8	**15b**	**11** (6)	1.2	50	$ZnCl_2$	72	100	**16d**	—	80
9	**15b**	**11** (6)	1.2	50	$ZnCl_2$	72	96	**16d**	—	64[c]
10	**15b**	**18** (6)	1.2	50	$ZnCl_2$	36	76	**16e/17e**	—	—[f]
11	**15b**	**18** (6)	1.6	50	$ZnCl_2$	36	100	**16e/17e**	35/65	70
12	**15b**	**9** (6)	1.6	50	EuFOD	36	69	**16f/17f**	58/42	48[g,h]
13	**15b**	**9** (6)	1.6	50	EuFOD	72	80	**16f/17f**	60/40	61[g,h]

[a] Unless otherwise indicated, 0.1 equiv of catalyst was used.
[b] Conversion.
[c] One equivalent of catalyst was used.
[d] Compound **19a** was isolated in 16% yield (see text).
[e] Complete degradation occured.
[f] Not isolated.
[g] Diasteromeric cycloadducts **20a** and **20b** were isolated after hydrolysis of the silyl enol ether.
[h] Compound **19b** was isolated in 15 and 18% yield, respectively (see text).

be the most reactive site. Thus treatment of pyrrole **7** with **9** (1.5 equiv) at room temperature led to a complete conversion after 20 h (Table 2, entry 1). Purification of the crude oil led to the isolation of cycloadduct **13** in a much better, 90% yield. The minor formation of bisadducts **14**, the result of two sequential hetero Diels–Alder processes, was also observed (5% isolated yield). Carrying out the reaction under a pressure of 1.2 GPa decreased the ratio **13**:**14** (entry 2). Attempts to maximize the formation of **14** involved the use of higher pressures, increasing the number of equivalents of diene, and activation by a Lewis acid. This led to the formation of a 45:55 mixture of **13**:**14**, which were separated by chromatography on silica (entry 3).

The exclusive hetero Diels–Alder processes arising from reactions between **7** and dienes **9** or **11** point to the low reactivity of the pyrrole carbon–carbon double bonds. Both aldehyde and ketoester carbonyl units have been reported to react as heterodienophiles and to constitute a useful access to dihydropyrans.[2] Although this reaction is in general much slower than the classical all-carbon Diels–Alder cycloaddition, it may become a competitive or exclusive pathway when the all-carbon dienophile becomes less reactive. Recently, work from this laboratory has shown that tenuous changes in electron-poor indoles may induce a complete reversal of chemoselectivity in their cycloaddition reactions with dienes.[8b]

The acetyl unit was next selected as electron withdrawing group. Indeed, literature data indicated that involvement of a simple ketone as heterodienophile is much less common.[2,13] Hence 2,4-diacetyl-1-*p*-tosylpyrrole (**15a**)[14,15] as singled out as the best available candidate to pursue the present study. Heating a toluene solution of **15a** and dimethylbutadiene **11** at 130 °C (pressure tube) for 7 days in the presence of zinc chloride (0.1 equiv) led to a 38% conversion (Table 3, entry 1). Purification of the crude resulting sample gave the all-carbon cycloadduct **16a** in low yield. However, this result was very encouraging as chemoselectivity and site selectivity in favor of the C_4,C_5 carbon–carbon double bond proved to be complete.[16] This result was in complete accordance with previous data gathered on indoles and furans.[6,8,11] The need for Lewis acid activation was verified by carrying out the same reaction in either the presence or the absence of zinc chloride under high pressure (entries 2 and 3).[17] Thus, conducting the reaction under a pressure of 1.2 GPa, at 50 °C and in the presence of the same Lewis acid led to a slightly higher conversion which, this time translated into an isolated yield of 40% (entry 3). Increasing the amount of $ZnCl_2$ to one full equivalent led to an optimized yield of 48% (entry 4). The use of cyclohexa-1,3-diene **18**, a four π-electron partner frozen in a *cisoid* conformation, led to essentially the same result, the expected diastereomeric cycloadducts **16b** and **17b** being isolated in moderate yield (entry 5). The relative stereochemistry was assigned according to NOESY experiments (Fig. 3). Interestingly, the major diastereomer produced in this case is the one defined as *exo*, that is corresponding to the approach where the dienic part and the β-acetyl group are superimposed.[18]



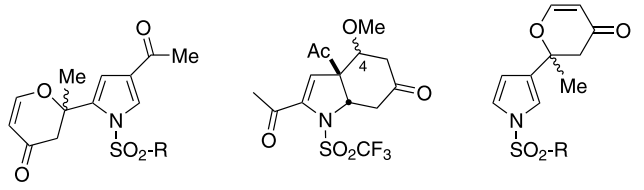
16b: R = *p*-Tol
16e: R = CF_3

17b: R = *p*-Tol
17e: R = CF_3

Figure 3. NOESY correlations observed on **16b** and **16e**, and **17b** and **17e**.

The reaction between **15a** and Danishefsky's diene **9** in the presence of EuFOD indicated a low conversion (entry 6). Purification of the crude mixture led to the isolation of a 1:1 adduct, whose analytical data pointed to structure **19a**, the result of an heterocycloaddition involving the carbonyl unit on position 2. Presumably, the electron-poor heterocycle acts as a global electron withdrawing substituent, thereby inducing the ketone behavior to parallel the known ketoester and ketoamide reactivities.[2,8b]

Attempts to further increase the reactivity and reverse the chemoselectivity in favor of the pyrrolyl C_2,C_3 carbon–carbon double bond included replacing the *p*-tosyl group with a trifluoromethanesulfonyl (triflyl) unit, a more powerful activating group.[19] Hence, pyrrole **15b** was prepared by interacting 2,3-diacetylpyrrole[15] with *N*,*N*-bistriflylphenylimide under basic conditions (78% isolated yield).[20] The



19a: R = *p*-Tolyl
19b: R = CF_3

20a : (4*R**) *endo*
20b : (4*S**) *exo*

24a: R = *p*-Tolyl
24b: R = CF_3

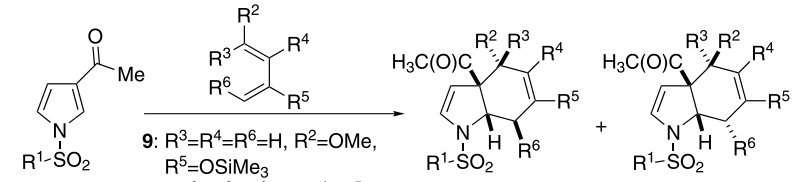
Figure 4. Structures of cycloadducts **19a**, **19b**, **20a**, **20b**, **24a** and **24b**.

thermal sensitivity of the substrate was highlighted by its complete degradation when heated at 130 °C in the presence of $ZnCl_2$ (entry 7). Activation by high pressures proved once again to be crucial. Thus subjecting substrate **15b** and 6 equiv of **11** to a pressure of 1.2 GPa at 50 °C and in the presence of $ZnCl_2$ led to a complete conversion and the regioselective formation of adduct **16d** (80% isolated yield) (entry 8). In the case of **15b**, increasing the amount of $ZnCl_2$ from 0.1 to 1 equiv resulted in a drop of the yield (compare entries 8 and 9). The reaction with cyclohexa-1,3-diene **18** illustrated once again the dramatic improvement induced by the triflyl group (entries 10 and 11). Optimized conditions led to a complete conversion and furnished a 70% isolated yield of a 35:65 mixture of *endo* and *exo* stereoisomers (**16e** and **17e**, respectively, entry 11), the latter being the major one. Reaction with the electronically enriched diene **9** yielded a 69% conversion after 36 h under 1.6 GPa, and 80% conversion after 72 h (entries 12 and 13). Hydrolysis generated a mixture of three adducts which were separated by chromatography. The two first adducts proved to be the expected *endo* and *exo* adducts resulting from reaction between the diene and the C_4=C_5 aromatic double bond (a 6:4 diastereomeric mixture), isolated as keto derivatives **20a** and **20b** in 48 and 61% yield (entries 12 and 13, respectively). Further elution afforded heterocycloadduct **19b** (15 and 18% isolated yield, respectively). In this case, the site selectivity was unambiguously determined by carrying out HMBC NMR experiments.

Thus the triflyl group did succeed in playing a dual role: not only does it increase the reactivity of the C_4,C_5 carbon–carbon double bond of the aromatic five-membered cycle, but, in addition, it is able to reverse the chemoselectivity, the carbon–carbon double bond being now the favor site of reactivity.

These results induced us to examine the effect of the triflyl group on the less reactive, monoacetylated pyrrole, and to compare it to the analogous tosylated substrate **21a** (Fig. 4).

Table 4. Cycloaddition between acetylpyrroles **21** and dienes **9**, **11** and **18**



9: R^3=R^4=R^6=H, R^2=OMe, R^5=$OSiMe_3$
11: R^2=R^3=R^6=H, R^4=R^5=Me
18: R^3=R^6= -CH_2-, R^2=R^4=R^5=H

21a: R^1 = *p*-Tolyl
21b: R^1 = CF_3

22 *endo*

23 *exo*

Entry	R^1	Diene (equiv)	*P* (GPa)	Cat.[a]	*t* (h)	Conv. (%)[b]	*endo*/*exo*	Yield (%)
1	*p*Tol	**11** (6)	1.2	$ZnCl_2$	36	Traces	—	—[c]
2	*p*Tol	**18** (6)	1.6	$ZnCl_2$	36	50	5/95	25
3	*p*Tol	**9** (6)	1.6	EuFOD	72	7	—	—[d]
4	CF_3	**11** (6)	1.2	$ZnCl_2$	36	31	—	24
5	CF_3	**11** (6)	1.6	$ZnCl_2$	36	91	—	80
6	CF_3	**18** (6)	1.6	$ZnCl_2$	36	97	13/87	49
7	CF_3	**9** (6)	1.6	EuFOD	72	23	—	—[e]

[a] 0.1 equiv of catalyst was used.
[b] Conversion.
[c] Not isolated.
[d] Compound **24a** was isolated in 7% yield.
[e] Compound **24b** was isolated in 15% yield.

Not surprisingly, reaction between the latter and any of the above diene (**9**, **11** or **18**) under hyperbaric conditions proved sluggish, delivering the desired adducts in 25% isolated yield, at best (Table 4, entries 1–3). Reaction of the corresponding triflyl derivative **21b**[21,22] with dimethylbutadiene, however, confirmed the above observations: under a pressure of 1.2 GPa and in the presence of 10% mol $ZnCl_2$, a 31% conversion was observed after 36 h, which became nearly quantitative when the same reaction was carried out under 1.6 GPa (entries 4 and 5). The desired cycloadduct **22a** was then isolated in 80% yield. A complete conversion was also obtained with cyclohexa-1,3-diene **18** and a 13:87 mixture of *endo*/*exo* cycloadducts were isolated in 49% yield (entry 6). The use of Danishefsky's diene, however, did not lead in this case to a reversal of chemoselectivity and heterocycloadduct **24b**, resulting from a pericyclic process involving the 3-carbonyl unit as the 2π component, was obtained in low yield (entry 7).[23]

The results described clearly indicate that similar levels of energy exist for the carbon–carbon double bond of aromatic pyrrole, when substituted by electron withdrawing substituents, on the one hand, and the acyl group of the substituent(s) in position 2 or 4, on the other hand. The structural and electronic nature of the diene definitely plays a role on the chemoselectivity of the reaction. The triflyl group, however, may counteract the tendency of electron-rich dienes to react in a hetero Diels–Alder fashion, and will induce in most cases the pyrrole C_2–C_3 double bond (1,3-disubstituted cases) or C_4–C_5 double bond (1,2,4-trisubstituted cases) to behave instead as the reacting dienophile.

3. Conclusion

The nature of the substituents on the *N*-tosylpyrrole nucleus plays a crucial role in the course of the cycloaddition reaction. Thus, formyl- and ketoester- substituted pyrroles undergo a hetero-Diels–Alder process resulting from their involvement as heterodienophiles, while the carbonyl group of unactivated ketones is almost inert, thereby allowing the aromatic carbon–carbon double bond of the pyrrole to behave as a dienophile—albeit in low yields. Biactivation by high pressures and Lewis acid leads to an increase in isolated yields. In this regard, replacement of the *p*-tosyl group with a triflyl one results in a dramatic change by further activating the latter reaction enough to afford good isolated yields of dearomatized cycloadducts encompassing a quaternary center at the ring junction. This methodology may now be used in the synthesis of natural and non-natural products, and in the production of scaffolds for the preparation of libraries.

4. Experimental

Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform relative to $(CH_3)_4Si$ and $CDCl_3$, respectively. Chemical shifts are expressed in parts per million (ppm). Low resolution and high-resolution mass spectra were recorded on Unicam ATI Automass and Jeol 500 spectrometers, respectively. IR spectra were recorded on Perkin–Elmer 16PC FT-IR spectrometers. The crude organic extracts were dried over magnesium sulfate. Unless otherwise stated, the products are colorless oils.

4.1. General procedure for the tosylation of pyrrole

A mixture of the pyrrole derivative (1 equiv), DMAP (cat.), $(^i Pr)_2EtN$ (1.3 equiv), and TsCl (1–1.3 equiv) was stirred at room temperature for 1 h under argon. After quenching with a 1 N HCl aqueous solution, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated under reduced pressure.

4.1.1. [5-Formyl-1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]-oxo-acetic acid methyl ester (7). Prepared according to the general procedure using (5-formyl-1*H*-pyrrol-3-yl)oxo-acetic acid, methyl ester (1.81 g, 10 mmol), DMAP (20 mg), $(^i Pr)_2EtN$ (2.26 mL, 13 mmol), and TsCl (1.91 g, 10 mmol) in CH_2Cl_2 (20 mL). The residue was purified by crystallization from CH_2Cl_2/heptane to give **7** as a white solid (2.80 g, 84%, mp 149 °C). ^{1}H NMR δ 2.44 (s, 3H), 3.98 (s, 3H), 7.38 (d, J=7.9 Hz, 2H), 7.65 (d, J=1.9 Hz, 1H), 7.91 (d, J=7.9 Hz, 2H), 8.64 (d, J=1.9 Hz, 1H), 9.90 (s, 1H). ^{13}C NMR δ 21.8, 53.3, 122.2, 124.2, 128.3 (2C), 130.3 (2C), 133.7, 135.3, 147.0 (2C), 161.3, 176.9, 178.4. IR (NaCl) ν 3360, 3154, 1728, 1682, 1548, 1380, 1180, 1146, 1052 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 335 [$M^{+\cdot}$] (5), 276 (100), 155 (78), 91 (94), 65 (29). HRMS calcd for $C_{21}H_{26}NO_4S$: ($M^{+\cdot}$) 335.0464. Found: 335.0451.

4.1.2. 1-[5-Acetyl-1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl] ethanone (15a). Prepared according to the general procedure using 1-(5-acetyl-1*H*-pyrrol-3-yl)-ethanone (0.76 g, 5 mmol), DMAP (10 mg), $(^i Pr)_2EtN$ (1.13 mL, 6.5 mmol), and TsCl (1.24 g, 6.5 mmol) in CH_2Cl_2 (10 mL). The residue was purified by chromatography on silica and elution with a mixture heptane/EtOAc (3:2) to give **15a** as a white solid (1.42 g, 93%, mp 170 °C). ^{1}H NMR δ 2.38 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 7.35 (d, J=7.9 Hz, 2H), 7.41 (d, J=1.9 Hz, 1H), 7.94 (d, J=7.9 Hz, 2H), 8.33 (d, J=1.9 Hz, 1H). ^{13}C NMR δ 21.5, 26.8, 27.0, 121.6, 125.3, 128.5 (2C), 129.3 (2C), 132.6, 133.8, 134.5, 145.4, 186.1, 191.9. IR (NaCl) ν 3334, 3144, 1682, 1552, 1470, 1362, 1126 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 305 [$M^{+\cdot}$] (6), 241 (28), 226 (20), 155 (48), 91 (100), 65 (21). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59; S, 10.50. Found: C, 59.46; H, 5.28; N, 4.67; S, 10.12.

4.1.3. 1-(5-Acetyl-1-trifluoromethanesulfonyl-1*H*-pyrrol-3-yl)ethanone (15b). A mixture of the pyrrole 1-(5-acetyl-1*H*-pyrrol-3-yl)-ethanone (0.61 g, 4 mmol), DMAP (20 mg), $(^i Pr)_2EtN$ (1.39 mL, 8 mmol), and $PhNTf_2$ (1.79 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred in CH_2Cl_2 (10 mL) at room temperature for 4 days under argon. After quenching with saturated aqueous $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica and elution with a mixture cyclohexane/EtOAc (9:1) to give **15b** as a white solid (0.88 g, 78%, mp 78 °C). ^{19}F NMR δ −67.42. ^{1}H NMR δ 2.51 (s, 3H), 2.54 (s, 3H), 7.52 (d, J=1.7 Hz, 1H), 8.01 (d,

$J=1.7$ Hz, 1H). ^{13}C NMR δ 26.8, 27.2, 117.3, 122.5, 127.7, 133.2, 135.8, 185.9, 191.2. IR (NaCl) ν 3132, 1686, 1416, 1212, 1132 cm^{-1}. MS (EI) *m/z* (relative intensity) 283 [$M^{+\cdot}$] (85), 268 (100), 118 (67), 69 (92). Anal. Calcd for $C_9H_8F_3NO_4S$: C, 38.17; H, 2.85; N, 4.95; S, 11.32. Found: C, 38.19; H, 2.74; N, 4.88; S, 11.41.

4.1.4. 1-(1-Trifluoromethanesulfonyl-1*H*-pyrrol-3-yl) ethanone (21b). A solution of 1-(1*H*-Pyrrol-3-yl)-ethanone (436 mg, 4 mmol) and (^{i}Pr)$_2$EtN (1.4 mL, 8 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C under argon. Triflic anhydride (845 μL, 5 mmol) was added dropwise, and after 30 min of stirring at the same temperature, the resultant solution was poured into 2 N NaOH aqueous solution and extracted with CH_2Cl_2. The combined organic layers were then poured into a 6 N HCl aqueous solution, stirred vigorously at room temperature for 15 min and finally extracted with CH_2Cl_2. Drying of the organic layers, filtration and evaporation under reduced pressure delivered the crude product which was immediately purified by Kügelrohr distillation (0.05 mmHg, 80–90 °C) to give an oil (761 mg, 79%, mp 34 °C) which crystallized upon standing. ^{19}F NMR δ −76.28. ^{1}H NMR δ 2.48 (s, 3H), 6.88 (m, 1H), 7.15 (m, 1H), 7.68 (m, 1H). ^{13}C NMR δ 27.4, 114.3, 118.9, 123.3, 125.8, 131.2, 192.0. IR (NaCl) ν 3129, 1687, 1235, 1210, 1153, 1060 cm^{-1}. MS (EI) *m/z* (relative intensity) 241 [$M^{+\cdot}$] (50), 226 (100), 142 (6), 93 (81), 69 (75). Anal. Calcd for $C_7H_6F_3NO_3S$: C, 34.86; H, 2.51; N, 5.81; S, 13.29. Found: C, 34.82; H, 2.55; N, 5.69; S, 13.26.

4.2. General procedure for the high-pressure reactions

Non-catalyzed reactions. To a solution of the requisite pyrrole, in dry dichloromethane (0.2 M) at room temperature under argon, was added the freshly distilled diene (6 equiv). The resultant mixture was transferred into a high-pressure vessel and compressed at the requisite pressure and temperature. After decompression, the solvent and excess diene were evaporated under reduced pressure. Chromatography of the residue on silica and elution led to the isolation of the cycloadduct(s).

The ketones resulting from hydrolysis of the silyl enol ether in the case of cycloadducts derived from Danishefsky diene were obtained in the following manner: after the reaction, removal of excess diene was achieved by bulb-to-bulb distillation under reduced pressure (50 °C/0.1 bar). The residue (0.3 mmol scale) was then stirred overnight in methanol (2 mL) in the presence of silica. Filtration and purification as above delivered the desired products.

4.3. Catalyzed reactions under high pressure

The experimental procedure is identical, except that the Lewis acid at room temperature was first added to the pyrrole solution. The mixture was stirred for 30 min and the diene (6 equiv) were added.

4.4. General procedure for thermal cycloadditions

A vessel containing the requisite pyrrole, the diene (12 equiv), hydroquinone (10 mg per mmol of substrate) in dry degassed toluene was sealed and heated in a sand bath behind a safety shield at the desired temperature. After cooling, the solvents and excess diene were removed under reduced pressure and the residue was chromatographed.

4.4.1. 2-[5-Formyl-1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]-4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (12). Elution with a mixture of heptane/EtOAc (4:1) gave the product. ^{1}H NMR δ 1.42 (s, 3H), 1.62 (s, 3H), 2.30 (d, $J=17.0$ Hz, 1H), 2.33 (s, 3H), 2.70 (d, $J=17.0$ Hz, 1H), 3.64 (s, 3H), 3.91 (d, $J=15.1$ Hz, 1H), 4.19 (d, $J=15.1$ Hz, 1H), 7.09 (d, $J=2.1$ Hz, 1H), 7.24 (d, $J=8.5$ Hz, 2H), 7.58 (d, $J=2.1$ Hz, 1H), 7.72 (d, $J=8.5$ Hz, 2H), 9.83 (s, 1H). ^{13}C NMR δ 13.6, 18.3, 21.6, 37.6, 52.6, 66.7, 75.6, 121.4, 121.9, 123.6, 126.2, 127.5 (2C), 128.1, 130.0 (2C), 133.2, 134.8, 146.0, 171.8, 178.7. IR (NaCl) ν 2922, 1738, 1674, 1378, 1178, 1092 cm^{-1}. MS (CI) *m/z* (relative intensity) 418 [MH^+] (100), 264 (14), 157 (11). HRMS calcd for $C_{21}H_{24}NO_6S$: (MH^+) 418.1324. Found: 418.1327.

4.4.2. 2-[5-Formyl-1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (13). Elution with a 3:2 mixture of heptane/EtOAc yielded cycloadduct **13**. ^{1}H NMR δ 2.37 (s, 3H), 2.93 (d, $J=16.8$ Hz, 1H), 3.25 (d, $J=16.8$ Hz, 1H), 3.71 (s, 3H), 5.43 (d, $J=6.0$ Hz, 1H), 7.10 (d, $J=1.9$ Hz, 1H), 7.29 (d, $J=7.9$ Hz, 2H), 7.35 (d, $J=6.0$ Hz, 1H), 7.64 (d, $J=1.9$ Hz, 1H), 7.76 (d, $J=7.9$ Hz, 2H), 9.87 (s, 1H). ^{13}C NMR δ 21.7, 43.9, 53.8, 81.9, 108.2, 120.9, 124.3, 126.1, 127.7 (2C), 130.3 (2C), 133.6, 134.5, 146.5, 160.9, 169.0, 178.6, 188.6. IR (NaCl) ν 2956, 1740, 1682, 1596, 1460, 1378, 1224, 1178, 1090 cm^{-1}. MS (CI) *m/z* (relative intensity) 404 [MH^+] (100). HRMS calcd for $C_{19}H_{18}NO_7S$: (MH^+) 404.0804. Found: 404.0806.

4.4.3. 4-Oxo-2-[5-(4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (14). Biscycloadduct was obtained by elution with a mixture of heptane/EtOAc (1:1) (two diastereomers). ^{1}H NMR δ 2.37 and 2.37 (s, 3H), 2.62 and 2.65 (dd, $J=4.1$, 17.0 Hz, 1H), 2.83 (dd, $J=12.8$, 17.0 Hz, 1H), 2.93 (d, $J=16.6$ Hz, 1/2H), 2.94 (d, $J=16.9$ Hz, ½H), 3.21 (d, $J=16.6$ Hz, ½H), 3.22 (d, $J=16.9$ Hz, ½H), 3.71 (s, 3H), 5.38–5.43 (m, 2H), 5.86 and 5.87 (dd, $J=4.1$, 12.8 Hz, 1H), 6.40 (m, 1H), 6.99 and 7.03 (d, $J=6.0$ Hz, 1H), 7.27 (d, $J=8.3$ Hz, 2H), 7.32 and 7.33 (d, $J=6.0$ Hz, 1H), 7.43 and 7.43 (d, $J=1.5$ Hz, 1H), 7.65 (d, $J=8.3$ Hz, 2H). ^{13}C NMR δ 21.6, 40.4 and 40.4, 43.6 and 43.7, 53.6, 71.7, 82.0, 107.5 and 108.0, 112.4 (2C), 122.1 and 122.2, 123.2 and 123.2, 127.1 and 127.2 (2C), 129.9 and 130.0 (2C), 131.4, 135.3, 145.8 and 145.8, 161.0 and 161.0, 161.5 and 161.7, 169.2 and 169.3, 188.9 and 188.9, 190.9. IR (NaCl) ν 3060, 1682, 1596, 1400, 1374, 1224, 1174, 1092, 1038 cm^{-1}. HRMS calcd for $C_{23}H_{22}NO_8S$: (MH^+) 472.1066. Found: 472.1046.

4.4.4. 1-[2-Acetyl-5,6-dimethyl-1-(toluene-4-sulfonyl)-1,4,7,7a-tetrahydroindol-3a-yl]ethanone (16a). Elution with a 7:3 mixture of heptane/EtOAc furnished derivative **16a**. ^{1}H NMR δ 1.53 (s, 3H), 1.58 (s, 3H), 1.77 (s, 3H), 1.96 (m, 2H), 2.14–2.24 (m, 1H), 2.32–2.46 (m, 1H), 2.35 (s, 3H), 2.39 (s, 3H), 4.33 (dd∼t, $J=4.1$ Hz, 1H), 5.40 (s, 1H), 7.23 (d, $J=7.9$ Hz, 2H), 7.46 (d, $J=7.9$ Hz, 2H). ^{13}C NMR

δ 19.4, 19.5, 21.6, 25.8, 28.7, 37.0, 37.6, 64.0, 64.7, 123.2, 125.1, 127.6, 128.5 (2C), 129.6 (2C), 130.8, 144.6, 147.4, 194.9, 206.0. IR (NaCl) ν 2926, 1702, 1354, 1166, 1090, 814, 660 cm^{-1}. HRMS calcd for $C_{21}H_{26}NO_4S$: (MH^+) 388.1583. Found: 388.1584.

4.4.5. 1-[4-Acetyl-3-(toluene-4-sulfonyl)-3-aza-tricyclo[5.2.2.0.^{2,6}]undeca-4,8-dien-6-yl]ethanone (16b/17b) Elution with a mixture of cyclohexane/EtOH (95:5) led to the isolation of the major, *exo* diastereomer **17b**. ^1H NMR δ 1.17–1.25 (m, 2H), 1.61–1.70 (m, 1H), 1.70 (s, 3H), 1.83–1.93 (m, 1H), 2.40 (s, 3H), 2.58 (s, 3H), 2.73–2.75 (m, 1H), 3.03–3.04 (m, 1H), 4.17 (d, J=3.0 Hz, 1H), 5.65 (s, 1H), 6.05 (dd∼t, J=7.3 Hz, 1H), 6.24 (dd∼t, J=7.3 Hz, 1H), 7.28 (d, J=8.3 Hz, 2H), 7.55 (d, J=8.3 Hz, 2H). ^{13}C NMR δ 16.8, 21.6, 21.8, 25.1, 28.4, 34.5, 34.7, 64.3, 66.5, 121.8, 128.3 (2C), 129.6 (2C), 131.2, 132.8, 132.9, 144.5, 146.0, 195.1, 202.9. IR (NaCl) ν 2946, 1701, 1615, 1597, 1354, 1164 cm^{-1}. MS (EI) *m/z* (relative intensity) 385 [$M^{+\bullet}$] (4), 264 (17), 187 (18), 155 (31), 91 (100). HRMS calcd for $C_{21}H_{24}NO_4S$: (MH^+) 386.1426. Found: 386.1410.

4.4.6. 1-(2-Acetyl-5,6-dimethyl-1-trifluoromethanesulfonyl-1,4,7,7a-tetrahydro-indol-3a-yl)ethanone (16d). Product **16d** was obtained by eluting with a 85:15 mixture of cyclohexane/EtOAc. ^{19}F NMR δ −71.68. ^1H NMR δ 1.65 (s, 3H), 1.76 (s, 3H), 2.17–2.41 (m, 4H), 2.26 (s, 3H), 2.33 (s, 3H), 5.11 (dd∼t, J=4.9 Hz, 1H), 5.81 (s, 1H). ^{13}C NMR δ 19.1, 19.4, 26.4, 28.1, 36.2, 36.9, 64.8, 65.4, 119.6, 125.4, 125.8, 126.6, 144.0, 190.3, 204.7. IR (NaCl) ν 2921, 1707, 1625, 1389, 1200, 1153 cm^{-1}. MS (EI) *m/z* (relative intensity) 366 [$M^{+\bullet}$] (15), 278 (63), 189 (50), 174 (45), 146 (100), 131 (36), 91 (40). Anal. Calcd for $C_{15}H_{18}F_3NO_4S$: C, 49.31; H, 4.97; N, 3.83; S, 8.78. Found: C, 49.24; H, 5.04; N, 3.79; S, 8.52.

4.4.7. 1-(4-Acetyl-3-trifluoromethanesulfonyl-3-azatricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-6-yl)ethanone (16e/17e). Elution with a 3:1 mixture of heptane/EtOAc delivered the major diastereomer **17e** (*exo*). ^{19}F NMR δ −71.09. ^1H NMR δ 1.30–1.80 (m, 4H), 2.21 (s, 3H), 2.43 (s, 3H), 2.98–3.02 (m, 2H), 4.90 (d, J=26 Hz, 1H), 5.90 (s, 1H), 6.17–6.30 (m, 2H). ^{13}C NMR δ 15.8, 21.9, 25.9, 28.0, 34.4 (2C), 66.1, 66.9, 120.0, 123.9, 132.2, 133.7, 143.3, 190.6, 202.6. IR (NaCl) ν 2953, 1707, 1617, 1390, 1199 cm^{-1}. MS (CI) *m/z* (relative intensity) 364 [MH^+] (100), 284 (8), 232 (13), 152 (10). HRMS calcd for $C_{15}H_{16}F_3NO_4S$: (MH^+) 364.0831. Found: 364.0826.

4.4.8. 2-[4-Acetyl-1-(toluene-4-sulfonyl)-1*H*-pyrrol-2-yl]-2-methyl-2,3-dihydro-pyran-4-one (19a). Eluent: cyclohexane/EtOAc (7:3). ^1H NMR δ 1.74 (s, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.82 (d, J=16.6 Hz, 1H), 2.94 (d, J=16.6 Hz, 1H), 5.43 (d, J=6.2 Hz, 1H), 6.97 (d, J=1.9 Hz, 1H), 7.25 (d, J=6.2 Hz, 1H), 7.32 (d, J=8.3 Hz, 2H), 7.74 (d, J=1.9 Hz, 1H), 7.88 (d, J=8.3 Hz, 2H). ^{13}C NMR δ 21.9, 27.2, 27.9, 47.3, 80.5, 106.8, 121.2, 126.7, 127.8, 128.7 (2C), 129.6 (2C), 133.8, 135.5, 145.3, 161.2, 186.2, 191.4. IR (NaCl) ν 2920, 1733, 1676, 1595, 1173 cm^{-1}. MS (EI) *m/z* (relative intensity) 373 [$M^{+\bullet}$] (21), 239 (16), 155 (30), 148 (32), 91 (100), 65 (31). HRMS calcd for $C_{19}H_{20}NO_5S$: (MH^+) 374.1062. Found: 374.1059.

4.4.9. 2-(4-Acetyl-1-trifluoromethanesulfonyl-1*H*-pyrrol-2-yl)-2-methyl-2,3-dihydro-pyran-4-one (19b). Eluted with mixtures of cyclohexane/EtOAc (7:3–3:7). ^{19}F NMR δ −68.17. ^1H NMR δ 1.73 (s, 3H), 2.50 (s, 3H), 2.83 (d, J=16.6 Hz, 1H), 2.92 (d, J=16.6 Hz, 1H), 5.46 (d, J=6.0 Hz, 1H), 7.11 (d, J=1.9 Hz, 1H), 7.26 (d, J=6.0 Hz, 1H), 7.42 (d, J=1.9 Hz, 1H). ^{13}C NMR δ 26.9, 27.3, 46.9, 79.9, 106.8, 119.5, 122.2, 126.8, 130.5, 135.6, 160.6, 185.5, 190.5. IR (NaCl) ν 2925, 1688, 1681, 1598, 1415, 1223 cm^{-1}. MS (CI) *m/z* (relative intensity) 352 [MH^+] (100), 251 (18), 220 (42). HRMS calcd for $C_{13}H_{12}F_3NO_5S$: (MH^+) 352.0466. Found: 352.0469.

4.4.10. 2,3a-Diacetyl-4-methoxy-1-trifluoromethanesulfonyl-1,3a,4,5,7,7a-hexahydro-indol-6-one (20a/20b). Elution with mixtures of cyclohexane/EtOAc (7:3–3:7) gave the major, *endo* diastereomer **20a**. ^{19}F NMR δ −72.21. ^1H NMR δ 2.32 (dd, J=9.8, 181 Hz, 1H), 2.35 (s, 3H), 2.39 (s, 3H), 2.70 (dd, J=5.7, 160 Hz, 1H), 2.74 (dd, J=4.5, 181 Hz, 1H), 2.78 (dd, J=4.9, 160 Hz, 1H), 3.32 (s, 3H), 4.08 (dd, J=4.5, 98 Hz, 1H), 5.17 (dd, J=4.9, 5.7 Hz, 1H), 6.26 (s, 1H). ^{13}C NMR δ 28.2, 29.4, 40.0, 43.4, 57.3, 63.7, 66.2, 77.4, 119.4, 121.8, 144.6, 189.9, 203.6, 206.8; IR (NaCl) ν 2925, 1712, 1624, 1602, 1391, 1211 cm^{-1}. MS (CI) *m/z* (relative intensity) 384 [MH^+] (100), 352 (32), 252 (82), 220 (11). HRMS calcd for $C_{14}H_{17}F_3NO_6S$: (MH^+) 384.0729. Found: 384.0732. Further elution delivered the minor, *exo* diastereomer **20b**. ^{19}F NMR δ −72.05. ^1H NMR δ 2.28 (dd, J=2.8, 185 Hz, 1H), 2.33 (s, 3H), 2.36 (s, 3H), 2.82 (dd, J=3.8, 185 Hz, 1H), 2.88 (d, J=41 Hz, 2H), 3.31 (s, 3H), 4.15 (dd, J=2.8, 38 Hz, 1H), 5.75 (t, J=4.1 Hz, 1H), 5.85 (s, 1H). ^{13}C NMR δ 25.9, 28.4, 37.5, 41.6, 57.2, 61.2, 66.4, 78.8, 118.8, 119.3, 144.9, 190.1, 199.7, 204.2. IR (NaCl) ν 2925, 1712, 1624, 1602, 1391, 1211 cm^{-1}. MS (CI) *m/z* (relative intensity) 384 [MH^+] (31), 352 (100), 252 (88), 220 (22). HRMS calcd for $C_{14}H_{17}F_3NO_6S$: (MH^+) 384.0729. Found: 384.0724.

4.4.11. 1-[3-(Toluene-4-sulfonyl)-3-aza-tricyclo[5.2.2.0^{2,6}]-undeca-4,8-dien-6-yl]-ethanone (22b/23b). Elution with a 3:2 mixture of cyclohexane/CH_2Cl_2 yielded the major, *exo* diastereomer **23b**. ^1H NMR δ 1.03–1.30 (m, 2H), 1.66–1.82 (m, 1H), 1.70 (s, 3H), 1.94–2.04 (m, 1H), 2.39 (s, 3H), 2.78 (dt, J=2.6, 5.2 Hz, 1H), 3.05–3.10 (m, 1H), 4.13 (dd, J=1.1, 3.8 Hz, 1H), 4.89 (d, J=4.1 Hz, 1H), 6.10–6.20 (m, 2H), 6.45 (d, J=4.1 Hz, 1H), 7.28 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.3 Hz, 2H). ^{13}C NMR δ 17.5, 21.6, 21.7, 25.1, 34.2, 34.6, 63.0, 69.6, 111.6, 127.6 (2C), 129.8 (2C), 132.7, 132.9, 133.7, 133.8, 144.1, 205.2. IR (NaCl) ν 2941, 1706, 1594, 1351, 1163 cm^{-1}. MS (CI) *m/z* (relative intensity) 344 [MH^+] (68), 264 (100), 154 (95), 136 (70), 91 (46). HRMS calcd for $C_{19}H_{22}NO_3S$: (MH^+) 344.1320. Found: 344.1328.

4.4.12. 1-(5,6-Dimethyl-1-trifluoromethanesulfonyl-1,4,7,7a-tetrahydroindol-3a-yl)-ethanone (22d). Obtained from elution with a 65:35 mixture of cyclohexane/CH_2Cl_2. ^{19}F NMR δ −73.76. ^1H NMR δ 1.68 (s, 3H), 1.74 (s, 3H), 2.15–2.33 (m, 3H), 2.23 (s, 3H), 2.50 (dd, J=4.7, 14.9 Hz, 1H), 4.97–5.03 (m, 1H), 5.15 (d, J=4.3 Hz, 1H), 6.28 (d, J=4.3 Hz, 1H). ^{13}C NMR δ 19.4, 19.7, 26.0, 36.0, 37.2, 62.9, 66.8, 114.4, 120.1, 126.1, 126.6, 130.6, 205.9. IR

(NaCl) ν 2916, 1712, 1398, 1227, 1192 cm^{-1}. HRMS calcd for $C_{13}H_{16}F_3NO_3S$: (MH^+) 324.0894. Found: 324.0881.

4.4.13. 1-(3-Trifluoromethanesulfonyl-3-azatricyclo-[5.2.2.0^{2,6}]undeca-4,8-dien-6-yl)-ethanone (22e/23e). The major diastereomer **23e** (*exo*) by elution with a 92:8 mixture of cyclohexane/EtOAc. ^{19}F NMR δ −74.24. ^1H NMR δ 1.09–1.36 (m, 2H), 1.76–1.82 (m, 2H), 2.17 (s, 3H), 2.95 (ddd∼dt, J=2.6, 5.1 Hz, 1H), 3.06–3.13 (m, 1H), 4.77 (dd, J=1.1, 2.6 Hz, 1H), 5.20 (d, J=4.1 Hz, 1H), 6.15–6.26 (m, 2H), 6.34 (d, J=4.1 Hz, 1H). ^{13}C NMR δ 16.6, 22.0, 25.5, 34.3 (2C), 64.4, 69.6, 113.3, 120.0, 130.4, 132.4, 133.8, 204.0. IR (NaCl) ν 2950, 1713, 1398, 1225, 1195 cm^{-1}. HRMS calcd for $C_{13}H_{14}F_3NO_3S$: ($M^{+\cdot}$) 321.0643. Found: 321.0646.

4.4.14. 2-Methyl-2-(1-trifluoromethanesulfonyl-1*H*-pyrrol-3-yl)-2,3-dihydro-pyran-4-one (24b). Elution with a 4:1 mixture of cyclohexane/EtOAc afforded the desired product. ^{19}F NMR δ −76.52. ^1H NMR δ 1.74 (s, 3H), 2.90 (d, J=16.6 Hz, 1H), 3.00 (d, J=16.6 Hz, 1H), 5.53 (d, J=6.0 Hz, 1H), 6.50 (dd, J=3.4, 1.5 Hz, 1H), 7.07–7.10 (m, 1H), 7.10–7.15 (m, 1H), 7.27 (d, J=6.0 Hz, 1H). ^{13}C NMR δ 27.3, 47.1, 80.3, 106.6, 113.7, 118.7, 119.0, 123.2, 133.5, 160.9, 191.3. IR (NaCl) ν 3142, 2982, 1677, 1597, 1419, 1233, 1209, 1147 cm^{-1}. MS (EI) m/z (relative intensity) 309 [$M^{+\cdot}$] (1), 239 (86), 148 (12), 104 (100). HRMS calcd for $C_{11}H_{11}NO_4S$: (MH^+) 310.0361. Found: 310.0355.

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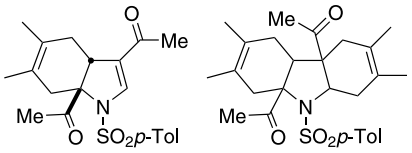
16. Examples of possible side-products include cycloadduct **i** and biscycloadduct **ii**; however, none of these were isolated, or even detected in the crude mixture.



i **ii**

17. Various Lewis acids (among which $AlMe_3$, $MeAlCl_2$, Me_2AlCl, $ZnCl_2$, EuFOD, for example) were checked for their abilities to catalyze the reaction. Zinc chloride proved to be the most efficient one.
18. *endo* Addition can be defined as 'that particular arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile', meaning the pyrrole part in this case[1c] In this precise case, the volume of the transition state leading to the *exo* diasteromer is probably more compact than the one delivering the *endo* cycloadduct.
19. Analogous reactions conducted with indole derivatives have shown the beneficial effect of the triflyl group, allowing the desired transformation to reach completion under milder conditions and in shorter times. Chataigner, I.; Piettre, S. R. Unpublished results.
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23. The exclusive site selectivity observed in the hetero Diels–Alder reaction of **15a** and **15b** to generate dihydropyrans **19a** and **19b**, respectively, in connection with the formation of **24a** and **24b**, seems to indicate the higher reactivity of an acyl group in α versus β position to the sulfonamide. Such a behavior might result from the possible chelation of the Lewis acid by both the reacting carbonyl group and the sulfonyl unit in the former case only.