Reactions of 1-Tosyl-3-substituted Indoles with Conjugated Dienes under Thermal and/or High-Pressure Conditions

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The behavior of 1-tosyl-3-acetylindole (**1a**), *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide (**1b**), and 1-tosyl-3-nitroindole (**1c**) as dienophiles in Diels−Alder reactions under thermal and/or high-pressure conditions was explored with different dienes: isoprene (**2**), 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene (**3**), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (**4**). Compared to the acylated indoles, the nitro derivative proved to be the best dienophile. In general, the use of Danishefsky's diene led to high-yielding reactions under milder conditions. Likewise, high-pressure conditions proved to be better in producing high yields of products. The advantage of high-pressure over thermal conditions was the ability of the former to generate highly functionalized adducts in better yields, which were otherwise very difficult or impossible to obtain. The use of thermal or high-pressure conditions led to different regio- and/or stereoselectivity in the adducts, allowing control of the regio- or stereoisomer produced.

Introduction

The versatile Diels−Alder [4 + 2] cycloaddition is an asset in the organic chemist's toolbox because it simultaneously sets ring(s), asymmetric centers, and functional groups.[1] Of the many parameters that could be changed to effect the success of a synthetic method, there is renewed interest in high pressure as a method to effect Diels−Alder reactions.[2] Since the Diels−Alder reaction is characterized by a negative volume of activation ($\Delta V^{\ddagger}$), the application of pressure facilitates the transformation of the reactants into the relatively more compact transition state, thereby lowering the activation energy of the process. Moreover, ΔV for the overall process is also negative, thus making it kinetically, as well as thermodynamically, favorable. At atmospheric pressure, some cycloadditions fail since they are reversible and reach a low equilibrium yield that cannot be improved by raising the temperature. Pressure, on the other hand, favors the forward reaction and disfavors the reverse, leading to higher yields.[3−5] Its use for preparative intermolecular Diels−Alder cycloadditions has been well studied,[2] but no successful examples of high-pressure Diels−Alder reactions involving heteroaromatic compounds as dienophiles have been reported.[6]

Recently, it has been shown that 1-tosyl-3-nitroindole (**1c**) is a very good dienophile in thermal Diels−Alder reactions (with normal electron demand) with different dienamides, leading to mixtures of 1-tosyl-4-substituted dihydrocarbazoles and 1-tosylcarbazoles. The ease of thermal extrusion of nitrous acid accompanying the reaction of this dienophile and the aromatization with *N*-alkylamide loss from the resultant dihydrocarbazoles (to produce highly stable heteroaromatic compounds) makes this two-step reaction sequence a facile, new method for dihydrocarbazole and carbazole synthesis.[7] Wenkert's previous observations have already demonstrated the feasibility of normal Diels−Alder chemistry with five-membered, aromatic heterocycles bearing electron-withdrawing groups, as dienophiles,[8] and the higher reactivity of β-substituted compared to α-substituted substrates.[9] Compounds such as furans, *N*-benzenesulfonylpyrroles, benzofurans, and *N*-benzenesulfonylindoles β-substituted with electron-withdrawing groups are involved as dienophiles in normal Diels−Alder reactions with 1,3-butadiene and isoprene, at elevated temperatures, leading to mixtures of regioisomers in moderate to high yields. The above-cited characteristics of the high-pressure conditions would lead to improved yields and eventual changes in the regio- and stereoselectivity of these cycloaddition reactions. Moreover, adducts would retain all of the substituents from the reactants, which

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(4) (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1−26. (b) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999−1027.

(5) Le Noble, W.; Kelm, H. *Angew. Chem.* **1980**, *19*, 841−856.

(6) The first indication of the advantages of high-pressure conditions in effecting Diels−Alder reactions of aromatic compounds acting as dienophiles is the reaction between 1-nitronaphthalene and Danishefsky's diene, which shows higher yields than the thermal reaction. Paredes, E.; Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **2000**, *41*, 8079−8082.

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(9) Despite much effort spent on the isolation of a 1:1 adduct in the methyl 1-tosyl-2-indolecarboxylate/isoprene reaction, none was observed. Under catalyzed conditions (50−90% of $AlCl_3$ or $BF_3{\cdot}Et_2O$, 100 °C, 24−120 h) the reaction afforded up to 15% of methyl 1-tosyl-3-prenyl-2-indolecarboxylate. Traces of an unknown product were also present, but the isolation was impossible to be carried out. NMR experiments of the crude led us to suppose the presence of a possible adduct.

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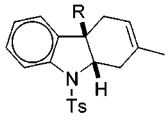
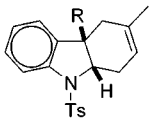
Table 1. Diels−Alder Reactions of 3-Acylindoles 1a and 1b with Isoprene (2)



5a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2



6a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2

entry	indole	diene	catalysis	reaction conditions	results[a]
1	**1a**	**2**, 12 equiv		20 °C, 10 kbar, 16 h	**5a**:**6a**, traces; **1a** 98%
2			$BF_3{\cdot}Et_2O$, 0.5 equiv	20 °C, 11 kbar, 16 h	**5a**, 55%; **1a**, 45%
3			$BF_3{\cdot}Et_2O$, 0.5 equiv	40 °C, 11.5 kbar, 72 h	**5a**, 46%; **1a**, 50%
4	**1b**	**2**, 12 equiv		40 °C, 11.5 kbar, 48 h	**5b**:**6b**, 20%; **1b**, 80%
5			$BF_3{\cdot}Et_2O$, 0.5 equiv	20 °C, 11.5 kbar, 16 h	**5b**, 72%; **1b**, 28%
6			$BF_3{\cdot}Et_2O$, 0.5 equiv	40 °C, 11.5 kbar, 72 h	**5b**, 55%; **1b**, 40%

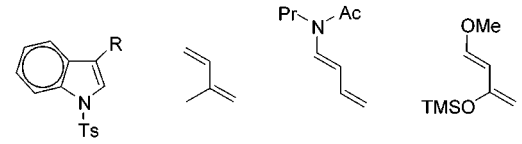
[a] Products, yield; dienophile, % recovery.

represents an advantage over the thermal Diels−Alder reaction of 1-tosyl-3-nitroindole (**1c**).

Accordingly, the purpose of the present work is to explore the behavior of 1-tosyl-3-acetylindole (**1a**), *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide (**1b**),[10] and 1-tosyl-3-nitroindole (**1c**) in normal Diels−Alder reactions with functionalized conjugated dienes. At the same time, this work aims at determining the regiochemistry and stereochemistry of the adducts obtained under thermal and/or high-pressure conditions, with a view to discussing the scope and limitations of this technique.

Results and Discussion

To test the efficacy of the Diels−Alder reaction of electron poor 1-tosylindoles, the following compounds were used as dienes: isoprene (**2**), 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene (**3**), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (**4**).

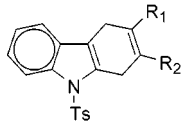


1a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2

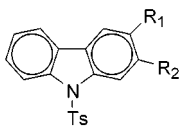
2 **3** **4**

When 1-tosyl-3-acetylindole (**1a**) and *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide (**1b**) were reacted with isoprene (**2**) under high pressures (Table 1, entries 1 and 4), mixtures of regioisomers **5a**, **6a** and **5b**, **6b** were obtained in very low yields. However, under catalyzed conditions (Table 1, entries 2 and 5), both reactions furnished over 50% of the single regioisomer **5a** and **5b**, respectively. Given the better electron-withdrawing properties of the glyoxylamide group, the yield of cycloadduct **5b** was ca. 15−20% higher than that of **5a**. Attempts to improve yields by increasing either the reaction time and/or the temperature only led to extensive diene polymerization, which prevented the complete recovery of the crude material from the reaction vessel. It was presumably due to this problem that the product conversion in these cases was lower (Table 1, entries 3 and 6). According to Wenkert,[8b] the reactions of both indoles with isoprene at 195 °C led to moderate-to-high yields (63−87%) of 3:1 mixtures of the above-mentioned regioisomers, whereas the Lewis acid catalysis of the reaction between 1-tosyl-3-acetylindole and isoprene during 4 h at 70 °C improved the regioselectivity (24:1 **5a**:**6a**) but lowered the yields (29%). These results demonstrated the higher capacity of the combination of high pressure/catalysis as compared to the combination of temperature/catalysis, in improving the yield and regioselectivity of the reaction.

Table 2. Diels-Alder Reactions of 3-Nitroindole 1c with Isoprene (2)



7- R_1 = H; R_2 = Me
8- R_1 = Me; R_2 = H



9- R_1 = H; R_2 = Me
10- R_1 = Me; R_2 = H
11- R_1 = H; R_2 = H
12- R_1 = H; R_2 = OH

entry	indole	diene	reaction conditions	results[a]
1	**1c**	**2**, 12 equiv	90 °C, 96 h	**7**:**8** (5:1), 30%; **1c**, 55%
2			20 °C, 11.5 kbar, 24 h	**5c**, 22%; **1c**, 77%
3			40 °C, 11.5 kbar, 72 h	**5c**, 75%; **9**, 5%; **1c**, 20%

[a] Products, yield; dienophile, % recovery.

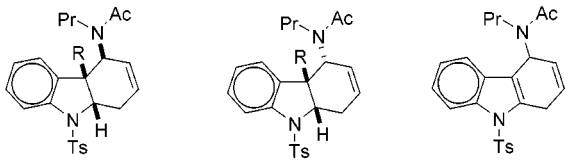
Attempts to produce the nitroadducts in the reaction between **1c** and **2** under mild thermal conditions[11] (Table 2, entry 1) were unsuccessful, with only 30% yield of regioisomeric dihydrocarbazoles **7** and **8** and no carbazoles produced. The reaction at high pressure gave a nitroadduct, single regioisomer **5c** in 22% yield (Table 2, entry 2). When the reaction was carried out at 40 °C during 72 h, the yield of **5c** reached 75%, with traces of carbazole **9** (Table 2, entry 3).[12] These results constituted

(10) Other choices as 1-tosyl-3-formylindole or methyl 1-tosyl-3-indoleglyoxylate were discarded due to both the lower reactivity as dienophiles and the higher instability under reaction conditions such as elevated temperatures or Lewis acid catalysis.

(11) Reproduction of Wenkert's reaction[8b] between 1-tosyl-3-nitroindole **1c** and isoprene **2** led to the same four-component mixture of dihydrocarbazoles **7** and **8** and carbazoles **9** and **10**.

(12) The presence of carbazole **9** was detected immediately following decompression by ^{1}H NMR analyses of the crude. The loss of nitrous acid could occur upon depressurization.

Table 3. Diels−Alder Reactions of 3-Acylindoles 1a and 1b with Dienamide 3



13a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2

14a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2

15

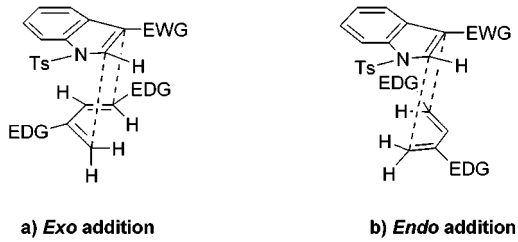
entry	indole	diene	reaction conditions	results[a]
1	**1a**	**3**, 3 equiv	40 °C, 10 kbar, 110 h	**13a**:**14a**, traces; **1a**, 80%
2	**1b**	**3**, 3 equiv	120 °C, 96 h	**13b**:**14b**, traces; **1b**, 73%
3			40 °C, 11.5 kbar, 48 h	**14b**, 51%; **1b**, 49%

[a] Products, yield; dienophile, % recovery.

the first indication of the advantages of high-pressure conditions in producing highly substituted products (even with a good leaving group such as nitro), impossible to obtain at normal pressure because of the thermal instability of the cycloadducts. In no case was the conversion into products complete, even under catalyzed conditions. Obviously, further increases of temperature, reaction time, or even pressure would result in more extensive polymerization of the diene and consequently a high viscosity, preventing the cycloaddition process from occurring.

Exposure of acylindole **1a** to 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene[13] (**3**) at different temperatures (110, 130, 160, and 200 °C) and reaction times (48, 192, 72, and 72 h, respectively) always led to the decomposition of both the diene (for temperatures above 150 °C) and/or the dienophile (for temperatures above 110 °C). Only for the glyoxylamide substitution on the indole was ca. 9% of a mixture of the possible diastereomeric cycloadducts **13b** and **14b** obtained (Table 3, entry 2).[14] The diene instability at elevated temperatures conspired against the success of the cycloaddition, even for the more reactive dienophile **1b**.[15]

The reactions were then carried out under high-pressure conditions. Considering the proven lower reactivity of the 1-tosyl-3-acetylindole (**1a**), the reaction was undertaken at 12 kbar during 110 h (Table 3, entry 1). However, the reaction led to only traces of a mixture of the possible adducts **13a** and **14a**.[14] Comparatively, at 12 kbar (Table 3, entry 3), dienophile **1b** and dienamide **3** underwent cycloaddition with the formation of ca. 51% of a single adduct **14b** with 49% recovery of dienophile. This reaction showed complete regio- and stereoselectivity, leading to one of four possible adducts. The steroisomer obtained constituted the first indication of an abnormal exo selectivity of the Diels−Alder reaction (Figure 1a). It could be thought that a transition state more compact than product could be responsible for the predisposition of the previously cited reaction to produce the exo adduct as the only product. Such speculation could be due to the unique feature of the secondary orbital interaction between the aromatic ring of the dienophile and the butadienic system of the diene, stronger than that expected between the glyoxylamide group and the dienic system.



a) *Exo* addition b) *Endo* addition

Figure 1. (a) Exo and (b) endo approaches of 1-tosyl-3-substituted indole and a substituted diene.

Previous results[7] showed the tendency toward thermal extrusion of nitrous acid in the reaction of 1-tosyl-3-nitroindole (**1c**) and dienamide **3** at temperatures higher than 90 °C. Attempts to produce the nitroadduct under milder thermal conditions (Table 4, entry 1) again led the substituted 1-tosyldihydrocarbazole **15**, the carbazole **11**, and the recovery of unreacted dienophile **1c**. In contrast to the reaction involving isoprene (**2**) under high-pressure conditions, the reaction of 1-tosyl-3-nitroindole (**1c**) and dienamide **3** at high pressures and 50 °C (Table 4, entry 2) led to the formation of the same substituted dihydrocarbazole **15** obtained under thermal conditions. Lowering the temperature and the diene/dienophile ratio, the reaction furnished a mixture of nitroadducts and dihydrocarbazole **15** (Table 4, entries 3 and 4). Due to the ease of nitrous acid extrusion, the chromatographic purification of the nitroadducts always led to mixtures with the corresponding dihydrocarbazole **15**, preventing the full identification of the former. Analyses of the mixture by ^{1}H NMR and ^{13}C NMR experiments and comparison with those of **14b** helped us to determine the structure of the main nitroadduct as **14c**.[16]

The use of Danishefsky's diene allowed us to analyze the influence of bulky substituents on the yields, regiochemistry and stereochemistry of the cycloadditions under thermal and/or high-pressure conditions. Heating a 12:1 mixture of **1a** and Danishefsky's diene **4** afforded only traces of a mixture of possible diastereomers **16a** and **17a**, after hydrolysis (Table 5, entry 1).[14] Attempts to increase the yields of the reaction under high-pressure conditions (Table 5, entries 2 and 3) led to only 25% of a ca. 1:1 (inseparable) mixture of the cited cycloadducts. Noteworthy, even under high pressure, this dienophile was not reactive enough to afford good yields in the reaction with a very good diene. Compared to acetylindole **1a**, glyoxylamide **1b** proved to be a far better dienophile, yielding a 40:1 mixture of diastereomers **16b** and **17b** in 70% yield at 120 °C after hydrolysis (Table 5, entry 4). The reaction showed a great preference for the endo

(13) A readily available dienamine, 1-(*N*,*N*-diethylamine)-1,3-butadiene, was also tested in thermal Diels−Alder reactions with 1-tosyl-3-formylindole, 1-tosyl-3-acetylindole, *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide, methyl 1-tosyl-3-indoleglyxolylate, and 1-tosyl-3-nitroindole, but the instability of the diene prevented the cycloaddition, with the formation of multiple byproducts, mainly the detosylated dienophiles in 30−50% yield.

(14) Detected by GC−MS analyses.

(15) 1-Tosyl-3-formylindole and methyl 1-tosyl-3-indoleglyoxylate were also tested in thermal Diels−Alder reactions with the above-mentioned dienamide, but their low reactivity/high thermal instability caused the failure of the cycloaddition and the decomposition of both the diene and the dienophile. Attempts to perform the reactions under Lewis acid catalysis conditions only led to complete diene decomposition.

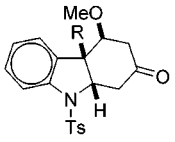
(16) Therefore HR-MS or elemental analyses were not possible to be performed.

Table 4. Diels–Alder Reactions of 3-Nitroindole 1c with Dienamide 3

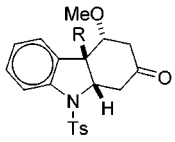
entry	indole	diene	reaction conditions	results[a]
1	**1c**	**3**, 3 equiv	65 °C, 48 h	**11**, 12%; **15**, 50%; **1c**, 20%
2		3 equiv	50 °C, 11.5 kbar, 30 h	**15**, 40%; **1c**, 20%
3		2 equiv	40 °C, 11.5 kbar, 40 h	**14c**, 25%; **15**, 50%; **1c**, 24%
4		1 equiv	40 °C, 11.5 kbar, 40 h	**14c**, 22%; **15**, 53%; **1c**, 24%
5		**18**, 3 equiv	65 °C, 48 h	**11**, 13%; **19**, 28%; **20**, 9%; **21**, 1%; **1c**, 49%

[a] Products, yield; dienophile, % recovery.

Table 5. Diels–Alder Reaction of 3-Acylindoles 1a and 1b with Danishefsky's Diene (4)



16a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2



17a- R = Ac
b- R = $COCONEt_2$
c- R = NO_2

entry	indole	diene	reaction conditions	results[a]
1	**1a**	**4**, 12 equiv	120 °C, 48 h	**16a**:**17a**, traces; **1a**, 75%
2		12 equiv	40 °C, 11.5 kbar, 48 h	**16a**:**17a** (1:1), 20%; **1a**, 80%
3		1 equiv	40 °C, 11.5 kbar, 48 h	**16a**:**17a** (1:1), 20%; **1a**, 80%
4	**1b**	**4**, 12 equiv	120 °C, 48 h	**16b**:**17b** (40:1), 71%; **1b**, 16%
5		12 equiv	40 °C, 11.5 kbar, 48 h	**16b**:**17b** (1:3.5),100%
6		1 equiv	40 °C, 11.5 kbar, 48 h	**16b**:**17b** (1:3.5), 100%
7		12 equiv	40 °C, 11.5 kbar, 20 h	**16b**:**17b** (1:3.5), 100%

[a] Products, yield; dienophile, % recovery.

Table 6. Diels–Alder Reaction of 3-Nitroindole 1c with Danishefsky's Diene (4)

entry	indole	diene	reaction conditions	results[a]
1	**1c**	**4**, 3 equiv	90 °C, 48 h	**12**, 47%; **16c**, 33%; **17c**, 4%; **1c**, 5%
2		3 equiv	65 °C, 24 h	**12**, 11%; **16c**, 32%; **17c**, 32%; **1c**, 20%
3		3 equiv	65 °C, 48 h	**12**, 17%, **16c**; 39%; **17c**, 25%; **1c**, 12%
4		12 equiv	40 °C, 11.5 kbar, 48 h	**16c**:**17c** (1:1), 100%
5		12 equiv	40 °C, 11.5 kbar, 6 h	**16c**:**17c** (1:1), 100%
6		1 equiv	40 °C, 11.5 kbar, 6 h	**16c**:**17c** (1:1), 100%

[a] Products, yield; dienophile, % recovery.

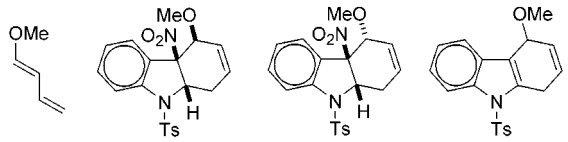
adduct **16b**. The application of high pressure to this reaction (Table 5, entries 5 and 6) led to quantitative conversion to a ca. 1:3.5 mixture of **16b** to **17b**. The optimal reaction time leading to quantitative yields was 20 h, working with a 1:1 diene/dienophile ratio. The inversion of the stereoselectivity in the thermal reaction demonstrated the potential of the trimethylsilyloxy and glyoxylamide groups in electronically and sterically directing the course of the reaction depending upon the pressure conditions. It is of interest to note that the trans arrangement of the glyoxylamide and methoxy groups was produced via the highly crowded exo transition state, which superimposed the trimethylsilyloxy group with the aromatic system of the indole. The diastereomeric excess of the exo isomer was attributed to the high pressures employed in the experiment, where steric effects were more easily overcome and the more compact exo transition state competed more favorably with its endo counterpart than at ambient pressures.

When 1-tosyl-3-nitroindole (**1c**) was reacted with Danishefsky's diene under thermal conditions (Table 6, entry 1), the reaction surprisingly afforded a 37% mixture of diastereomeric cycloadducts **16c** and **17c** in a 30:1 ratio after hydrolysis, with 48% of hydroxycarbazole **12**. When the reaction temperature was lowered to 65 °C (Table 6, entry 2), the isomeric ratio changed to ca. 1:1, with only 11% of hydroxycarbazole **12**. This result demonstrated that isomer **17c** is more likely to suffer thermal aromatization because of the trans arrangement of its nitro and methoxy substituents. The intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in either case. In a similar behavior pattern, the reaction carried out under high-pressure conditions (Table 6, entry 4) now gave a quantitative conversion of the dienophile into a ca. 1:1 mixture of the above named cycloadducts. Under these conditions, no hydroxycarbazole **12** was formed.[17] Optimization studies (Table 6, entries 5 and 6) found that the best conditions were 6 h and 40 °C (1:1 diene/dienophile ratio), affording quantitative conversion of dienophile, thus evidencing the higher reactivity of 1-tosyl-3-nitroindole (**1c**) compared to the glyoxylamide derivative **1b**. These reactions were completely regioselective. The results obtained at high pressure are in agreement with those obtained for substrate **1b** and Danieshefsky's diene under similar reaction conditions. The results obtained under thermal conditions could be due to the similarities in conformation and activation energy of both transition states. This means that the thermal reaction could overcome the steric effect of the trimethylsilyloxy group to produce the trans adduct **17c**. Furthermore, the electrostatic repul-

(17) The sample had to be worked up immediately after decompression, eliminating the excess of diene, otherwise a high proportion of carbazole was produced, showing the possibility of nitrous acid extrusion and aromatization after decompression, presumably induced by the excess of diene or the decomposition of the excess of diene.

sion between the strong negative charge of the nitro and the negative charge on the oxygen of the OTMS group in Danishefsky's diene in the endo transition state (Figure 1b) could constitute an additional factor leading to a high proportion of **17c**.[18]

To analyze the apparently different behavior of nitroadducts **5c**, **13**/**14c**, and **16**/**17c**, the thermal reaction between **1c** and 1-methoxy-1,3-butadiene **18** was undertaken (Table 4, entry 5). Nitroadducts **19** and **20** were isolated in good yields, carbazole **11** was formed in 13%, and only traces of the 4-substituted dihydrocarbazole **21** were detected. These results not only demonstrated the tendency toward thermal extrusion of nitrous acid from **14c** and the relative stability of the 4-substituted dihydrocarbazole **15** but also predicted the stereochemical course of the reactions involving **1c** and **3**. The thermal reaction would lead to a great excess of **13c**, which subsequently, would eliminate nitrous acid to produce dihydrocarbazole **15**. However, the high-pressure reactions could produce a mixture of **13c** and **14c**, which at low temperatures would lead to the observed mixture of **14c** and **15**. The extent of formation of the substituted 1-tosyldihydrocarbazole **15** would strongly depend on the structural arrangement between the nitro and *N*-acetyl-*N*-alkylamide groups (understood as cis or trans isomerism). However, when Danishefsky's diene (or 1-methoxy-1,3-butadiene) was involved in the cycloaddition process, the original adduct was very stable, under both high-pressure and high-temperature conditions. When the nitrous acid extrusion occurred, it was accompanied by loss of methanol, leading to the aromatic hydroxycarbazole **12**. The intermediate that suffered nitrous acid extrusion and retained the methoxy group was not detected in either case. In the thermal reaction with Danishefsky's diene, the nitrous acid extrusion and methanol elimination would presumably be produced during the process of silylenol ether hydrolysis,[19] in a concerted manner. In this case, the excess of diene or the nucleophilic trimethylsilyloxy produced in the absence of acid during the reaction would induce the whole process.



18 **19** **20** **21**

As a general conclusion, high-pressure conditions proved to be better in producing high yields of products and affording fully substituted adducts. On the other hand, the thermal reactions needed longer reaction times and higher temperatures and diene:dienophile ratios, to get acceptable yields. These could not be raised unless lower temperatures and very long periods of reaction were chosen. The use of either thermal of high-pressure conditions led to changes in the regio- and/or stereoselectivity of adducts, allowing control of the regio- or stereoisomer produced.

(18) Node M.; Nishide, K.; Imazato, H.; Kurosake, R.; Inoue, T.; Ikariya T. *Chem. Commun.* **1996**, 2559−2560.

(19) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris J. *J. Am. Chem. Soc.* **1979**, *101*, 6996−7000.

Experimental Section

General Aspects. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on 200 and 50, 300 and 75, and 400 and 100 MHz FT-spectrometers, respectively, using TMS as the internal standard; coupling constants (*J*) are given in Hz. GC analyses were performed on a PE-5-type column (30 m, 0.53 mm i.d., 0.5 μm coating). GC/MS analyses were performed in an instrument equipped with a similar column. Transmission IR spectra were recorded from NaCl cells as CCl_4 solutions. Melting points were observed on a Winkle-Zeiss Gottingen microhot stage and were uncorrected. The silica gel and neutral alumina used for chromatography were 70−230 mesh. The following reagents were prepared by literature methods: 1-tosyl-3-acetylindole (**1a**),[8b] *N*,*N*-diethyl-1-tosyl-3-indoleglyoxylamide (**1b**),[8b] 1-tosyl-3-nitroindole (**1c**),[7] 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene (**3**).[7] Other reagents were obtained from commercial sources and were used as received or purified as required by standard methods. The high-pressure reactions were performed in a Unipress piston-cylinder apparatus for pressures up to 14 kbar. The instrument allowed the possibility of simultaneously working with 4 pressure vessels, 1 mL each. All reactions were carried out in a nitrogen or argon atmosphere.

General Procedure for the Thermal Cycloaddition Reactions of Indoles. The temperature, the length of the reaction and the diene/dienophile ratio were dependent on the starting material. An ampule containing a solution of 1.0 mmol of the dienophile and the required amount of diene in 0.5 mL of dry benzene was cooled in liquid nitrogen, sealed, and then heated in an oil bath. After the reaction time was completed, it was cooled once more in liquid nitrogen and opened. The solution was evaporated and the residue purified by column chromatography on silica gel or alumina using hexane/ethyl acetate mixtures as eluent.

General Procedure for the High-Pressure Cycloaddition Reactions of Indoles. The temperature, the length of the reaction, and the diene/dienophile ratio were dependent on the starting material. Under an atmosphere of argon, neat diene was added to a pressure vessel containing 0.25 mmol of the dienophile, and the volume was completed with dry dichloromethane. The vial was then pressurized and heated to the required temperature for the desired reaction time. (CAUTION: depending upon the type of high-pressure apparatus being used, when heating the reaction attention must be paid to the increase of pressure. To avoid exceeding the safe operating window, the apparatus should not be fully pressurized, and after reaching the required temperature, minor adjustments should be done to keep the desired pressure). After the reaction time was completed, the equipment was allowed to cool to room temperature and then slowly decompressed. The solvent was then evaporated, the crude material was analyzed by ^{1}H and ^{13}C NMR and then chromatographed on silica gel or alumina with heptane/ethyl acetate mixtures as eluent. For the catalyzed reaction, a 0.4 M solution of BF_3·Et_2O in dry CH_2Cl_2 was added dropwise to the dienophile, the solution was stirred for 15 min, the diene was added, and the volume was completed with dry CH_2Cl_2. After decompression, the crude reaction mixture was quenched with 5 mL of a 10% aqueous solution of NH_4Cl, the organic phase was separated, and the aqueous solution was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated.

(±)-4a*β*-Acetyl-2-methyl-9-tosyl-1,4,4a,9a*β*-tetrahydro-9*H*-carbazole (5a) and 4a*β*-Acetyl-3-methyl-9-tosyl-1,4,-4a,9a*β*-tetrahydro-9*H*-carbazole (6a). Elution with 5:1 hexanes−ethyl acetate (on silica gel) led to the recovery of starting dienophile **1a**. Earlier fractions afforded traces of a mixture of **5a** and **6a** or only **5a** in the high-pressure BF_3-catalyzed reaction. Both of the homologous benzenesulfonylated derivatives were reported by Wenkert.[8b]

(±)-4a*β*-(*N*,*N*-Diethylglyoxylamido)-2-methyl-9-tosyl-1,4,4a,9a*β*-tetrahydro-9*H*-carbazole (5b) and 4a*β*-(*N*,*N*-Diethylglyoxylamido)-3-methyl-9-tosyl-1,4,4a,9a*β*-tetrahydro-9*H*-carbazole (6b). Elution with 5:1 hexanes−ethyl acetate (on silica gel) led to the recovery of starting dienophile

1b. Earlier fractions afforded traces of a mixture of **5b** and **6b** or only **5b** in the high-pressure BF_3-catalyzed reaction. Both of the homologous benzenesulfonylated derivatives were reported by Wenkert.[8b]

(±)-2-Methyl-4a*β*-nitro-9-tosyl-1,4,4a,9a*β*-tetrahydro-9*H*-carbazole (5c). Elution with 20:1 heptane−ethyl acetate (on silica gel) led to the recovery of unreacted dienophile **1c**. Earlier fractions afforded the nitroadduct **5c**: IR 1560, 1600, 1362, 1170 cm^{-1}; ^1H NMR (200 MHz) δ 1.80 (s, 3 H), 2.32 (s, 3 H), 2.50−2.58 (dd, 1 H, J = 15.4, 6.2), 2.68−2.75 (dd, 1 H, J = 15.4, 4.8), 2.75−2.83 (dd, 1 H, J = 15.4, 6.2), 2.99−3.04 (dd, 1 H, J = 15.4, 4.8), 4.98 (t, 1 H, J = 6.2), 5.42 (br t, 1 H), 7.08 (t, 1 H, J = 7.5), 7.16 (d, 2 H, J = 8.1), 7.28−7.39 (m, 2 H), 7.61 (d, 2 H, J = 8.1), 7.62 (d, 1 H, J = 7.5); ^{13}C NMR (50 MHz) δ 21.6, 23.0, 33.4, 35.8, 66.0, 96.2, 116.0, 118.0, 124.7, 125.2, 127.4, 129.7, 131.6, 133.6, 137.6, 143.6, 144.6. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C 62.48; H 5.24; N 7.29; S 8.34. Found: C 61.88; H 5.33; N 7.39; S 8.45. Compound **5c** had to be immediately analyzed; otherwise, it rapidly decomposed into carbazole **9**.

2-Methyl-9-tosyl-1,4-dihydro-9*H*-carbazole (7), 3-Methyl-9-tosyl-1,4-dihydro-9*H*-carbazole (8), 2-Methyl-9-tosyl-9*H*-carbazole (9), and 3-Methyl-9-tosyl-9*H*-carbazole (10). Elution with 25:1 hexanes−ethyl acetate (on silica gel) led to the recovery of unreacted dienophile **1c**. Earlier fractions afforded a 5:1 mixture of **7** and **8**, and a second fraction a 5:1 mixture of **9** and **10**. All the homologous benzenesulfonylated derivatives were reported by Wenkert.[8b,11]

(±)-4a*β*-(*N*,*N*-Diethylglyoxylamido)-4α-(*N*-propylacetylamino)-9-tosyl-1,4*β*,4a,9a*β*-tetrahydro-9*H*-carbazole (14b). For the high-pressure reaction, elution with 2:1 heptane−ethyl ether (on silica gel) led to the recovery of unreacted diene **3**, unreacted dienophile **1b**, and finally to **14b** as a light yellow solid: mp 155 °C; IR 1705, 1645, 1630, 1599, 1360, 1171 cm^{-1}; ^1H NMR (200 MHz) δ 0.74 (t, 3 H, J = 7.3), 0.93 (t, 3 H, J = 7.0), 1.05 (t, 3 H, J = 7.2), 1.25 (m, 1 H), 1.40 (m, 1 H), 1.77 (s, 3 H), 2.34 (s, 3 H), 2.25−2.35 (m, 2 H), 2.55−2.75 (m, 1 H), 2.92 (dm, 1 H, J = 17.0), 3.12 (m, 2 H), 3.28 (m, 2 H), 4.71 (dd, 1 H, J = 6.8, 3.4), 5.78 (dm, 1 H, J = 10.0), 5.80 (br s, 1 H), 6.15 (m, 1 H), 6.85−7.00 (m, 1 H),7.22−7.30 (m, 2 H), 7.20 (d, 2 H, J = 8.0), 7.62 (d, 2 H, J = 8.0), 7.70−7.85 (m, 1 H); ^{13}C NMR (75 MHz) δ 11.8, 12.7, 14.0, 21.9, 22.1, 24.9, 27.4, 39.8, 42.5, 48.6, 52.4, 63.4, 65.0, 115.6, 124.7, 125.4, 126.7, 128.2, 129.3, 129.8, 130.1, 133.2, 143.8, 144.8, 165.3, 172.4, 198.8. The main crystallographic parameters for this adduct are available in the Supporting Information.

9-Tosyl-9-*H*-carbazole (11),[7] (±)-4a*β*-Nitro-4α-(*N*-propylacetylamino)-9-tosyl-1,4*β*,4a,9a*β*-tetrahydro-9*H*-carbazole (14c), and (±)-4-(*N*-Propylacetylamino)-9-tosyl-1,4-dihydro-9*H*-carbazole (15).[7] Elution with 15:1 hexanes−ethyl acetate (on alumina) led to a first fraction of **11**, then a second fraction of unreacted indole **1c**, and finally the dihydrocarbazole **15** for the thermal reaction or a mixture of **14c** and **15** for the high-pressure reactions. Compounds **11** and **15** were previously characterized.[7] Due to nitrous acid elimination produced by chromatography on neutral alumina, compound **14c** could not be isolated, and consequently, it could not be fully characterized.[16] Selected spectral data for **14c**: IR 1652, 1600, 1590, 1371, 1158 cm^{-1}; ^1H NMR (200 MHz) δ 0.92 (t, 3 H, J = 7.7), 1.60 (m, 2 H), 2.05 (s, 3 H), 2.35 (s, 3 H), 3.10 (m, 2 H), 3.1−3.25 y 3.25−3.35 (dm, 2 H, J = 18.0), 5.53 (dm, 1 H, J = 9.5, 5.3), 5.69 (dd, 1 H, J = 9.1, 4.0; m, 1 H), 6.05 (dm, 1 H, J = 9.5), 7.1−7.8 (m, 7 H), 8.37 (d, 1 H); ^{13}C NMR (75 MHz) δ 11.5, 22.1, 22.3, 22.5, 23.6, 41.1, 61.9, 68.9, 97.0, 171.1.

(±)-4a*β*-Acetyl-4*β*-methoxy-2-oxo-9-tosyl-1,2,3,4α,4a,-9a*β*-hexahydro-9*H*-carbazole (16a) and (±)-4a*β*-Acetyl-4α-methoxy-2-oxo-9-tosyl-1,2,3,4*β*,4a,9a*β*-hexahydro-9*H*-carbazole (17a). For the high-pressure reaction, elution with 5:1 hexanes−ethyl acetate (on alumina) led to the recovery of unreacted dienophile, and further elution afforded a 1:1 mixture of diastereomers **16a** and **17a**, which were not separated: IR 1716, 1600, 1361, 1168 cm^{-1}. Selected data for **16a**: ^1H NMR (400 MHz) δ 2.07 (s, 3 H), 2.34 (s, 3 H), 3.31 (s, 3 H), 4.25 (t, 1 H), 5.45 (dd, 1 H). **17a**: ^1H NMR (400 MHz) δ 1.37 (s, 3 H), 2.34 (s, 3 H), 3.27 (s, 3 H), 4.27 (dd, 1 H), 4.69 (dd, 1 H).

(±)-4a*β*-(*N*,*N*-Diethylglyoxylamido)-4*β*-methoxy-2-oxo-9-tosyl-1,2,3,4α,4a,9a*β*-hexahydro-9*H*-carbazole (16b) and (±)-4a*β*-(*N*,*N*-Diethylglyoxylamido)-4α-methoxy-2-oxo-9-tosyl-1,2,3,4*β*,4a,9a*β*-hexahydro-9*H*-carbazole (17b). Elution with 5:1 hexanes−ethyl acetate (on alumina) led to the recovery of unreacted dienophile, and further elution afforded **16b** and **17b** in two consecutive fractions. IR 1720, 1636, 1600, 1361, 1168 cm^{-1}. **16b**: ^1H NMR (200 MHz) δ 0.67 (t, 3 H, J = 7.2), 1.12 (t, 3 H, J = 7.2), 1.94 (dd, 1 H, J = 18.0, 2.2), 2.10−2.30 (m, 1 H), 2.25−2.45 (m, 1 H), 2.64 (dd, 1 H, J = 18.0, 3.3), 2.34 (s, 3 H), 3.08 (dd, 1 H, J = 17.0, 5.6), 3.23 (dd, 1 H, J = 17.0, 2.2), 3.33 (s, 3 H), 3.15−3.35 (dm, 2 H), 3.30−3.50 (dm, 2 H), 4.75 (dd, 1 H, J = 3.3, 2.2), 5.48 (dd, 1 H, J = 5.6, 2.2), 7.03 (td, 1 H, J = 7.6, 1.1), 7.30 (dt, 1 H, J = 7.6, 1.3), 7.22 (d, 2 H, J = 8.3), 7.49 (d, 1 H, J = 6.9), 7.66 (d, 1 H, J = 8.0), 7.73 (d, 2 H, J = 8.3); ^{13}C NMR (50 MHz) δ 12.1, 13.1, 21.3, 37.2, 38.9, 41.2, 44.1, 56.5, 60.8, 63.7, 80.2, 115.9, 124.5, 126.0, 127.3, 127.7, 129.4, 130.5, 133.6, 141.9, 144.2, 164.9, 194.6, 206.4. **17b**: ^1H NMR (200 MHz) δ 0.75 (t, 3 H, J = 7.0), 1.12 (t, 3 H, J = 7.0), 2.28 (dd, 1 H, J = 18.0, 8.2), 2.56 (dd, 1 H, J = 18.0, 3.7), 2.35 (s, 3 H), 2.55 (m, 2 H), 3.09 (d, 2 H, J = 4.1), 3.26 (s, 3 H), 3.10−3.30 (m, 2 H), 3.35−3.55 (m, 2 H), 4.87 (dd, 1 H, J = 8.2, 3.7), 5.27 (t, 1 H, J = 4.1), 7.06 (td, 1 H, J = 7.4, 0.8), 7.30−7.40 (m, 2 H), 7.20 (d, 2 H, J = 8.0), 7.65 (d, 2 H, J = 8.0), 7.70 (d, 1 H, J = 8.0); ^{13}C NMR (50 MHz) δ 12.1, 13.1, 21.3, 38.4, 39.4, 41.3, 44.4, 57.0, 61.2, 64.4, 80.1, 115.4, 124.1, 127.6, 127.8, 127.3, 129.4, 130.0, 133.7, 142.3, 144.2, 165.1, 197.2, 205.5; MS (CI) m/z 499 (M + 1, 28), 370 (11), 201 (55), 343 (76), 100 (100) 72 (75); HRMS analysis (CI) m/z calcd for $C_{26}H_{30}N_2O_6S$ = 498.1825, found $(M + 1)^+$ = 499.1868, M^+ = 498.1845.

2-Hydroxy-9-tosyl-9*H*-carbazole (12), (±)-4*β*-Methoxy-4a*β*-nitro-2-oxo-9-tosyl-1,2,3,4α,4a,9a*β*-hexahydro-9*H*-carbazole (16c), and (±)-4α-Methoxy-4a*β*-nitro-2-oxo-9-tosyl-1,2,3,4*β*,4a,9a*β*-hexahydro-9*H*-carbazole (17c). Elution with 6:1 hexanes−ethyl acetate (on alumina) led to a first fraction containing the hydroxycarbazole **12** (for the thermal reactions) and a second fraction containing the unreacted dienophile **1c** (for the thermal reactions), and further elution afforded consecutively **16c** and **17c**. **12**: pale yellow plates; mp 41−41.5 °C; IR 3200, 1377, 1173 cm^{-1}; ^1H NMR (200 MHz) δ 2.21 (s, 3 H), 6.89 (dd, 1 H, J = 8.2, 2.4), 7.04 (d, 2 H, J = 8.0), 7.24−7.38 (m, 2 H), 7.67−7.78 (m, 2 H), 7.66 (d, 2 H, J = 8.0), 7.83 (d, 1 H, J = 2.1), 8.22 (dd, 1 H, J = 7.5, 1.2); ^{13}C NMR (50 MHz) δ 21.2, 101.8, 112.6, 114.8, 118.9, 119.4, 120.7, 123.8, 125.8, 126.3, 127.6, 129.5, 134.6, 138.0, 139.5, 144.7, 156.1. **16c**: white plates; mp 110 °C dec; IR 1728, 1599, 1558, 1466, 1362, 1326, 1265, 1171, 1092 cm^{-1}; ^1H NMR (200 MHz) δ 1.9 (dd, 1 H, J = 18.9, 2.5), 2.35 (s, 3 H), 2.67 (dd, 1 H, J = 18.9, 3.0), 3.26 (d, 2 H, J = 4.3), 3.35 (s, 3 H), 4.65 (br t, 1 H), 5.77 (t, 1 H), 7.05−7.25 (m, 1 H), 7.20 (d, 2 H, J = 7.9) 7.40−7.50 (m, 1 H), 7.54 (d, 1 H, J = 8.2), 7.66 (d, 2 H, J = 7.9) 7.73 (d, 1 H, J = 9.6); ^{13}C NMR (50 MHz) δ 21.5, 37.4, 43.9, 58.0, 61.4, 80.2, 90.4, 116.5, 124.9, 125.0, 125.2, 127.5, 129.7, 132.7, 132.9, 142.4, 145.0, 204.0. **17c**: white needles; mp 108−109 °C; IR 1732, 1596, 1556, 1466, 1362, 1269, 1171, 1090 cm^{-1}; ^1H NMR (200 MHz) δ 2.06 (dd, 1 H, J = 18.4, 10.0), 2.34 (s, 3 H), 2.72 (dd, 1 H, J = 18.4, 4.5), 3.10 (dd, 2 H, J = 5.5, 2.0), 3.33 (s, 3 H), 4.69 (dd, 1 H), 5.10 (br t, 1 H), 7.15 (d, 2 H, J = 8.1), 7.15−7.25 (m, 1 H), 7.47 (d, 2 H, J = 8.1), 7.40−7.55 (m, 1 H), 7.6 (d, 1 H, J = 7.6), 7.74 (d, 1 H, J = 8.9); ^{13}C NMR (50 MHz) δ 21.4, 39.9, 44.3, 58.0, 63.3, 77.8, 96.7, 116.7, 123.3, 125.0, 126.9, 129.4, 129.7, 132.3, 132.6, 143.0, 145.1, 202.7. The main crystallographic parameters for this adduct are available in the Supporting Information.

(±)-4*β*-Methoxy-4a*β*-nitro-9-tosyl-1,4α,4a,9a*β*-tetrahydro-9*H*-carbazole (19), (±)-4α-Methoxy-4a*β*-nitro-9-tosyl-1,4*β*,4a,9a*β*-tetrahydro-9*H*-carbazole (20), and (±)-4-Methoxy-9-tosyl-1,4-dihydro-9*H*-carbazole (21). Elution with 15:1 hexanes−ethyl acetate (on alumina) led to a first fraction containing the carbazole **11**,[7] a second fraction containing a mixture of **19** and **21** (which were not separated due

to the ease of nitrous acid extrusion from **19**, which readily decomposed to form **21**), and then a third fraction containing the unreacted dienophile **1c** and finally **20**. Selected data for **19**: IR 1600, 1558, 1360, 1172 cm^{-1}; ^1H NMR (200 MHz) δ 2.24 (s, 3 H), 2.76−2.79 and 2.82−2.87 (ddd, 1 H, J = 16.4, 6.6, 2.7), 2.91−2.97 and 2.99−3.06 (two m, 1 H, J = 3.0), 3.20 (s, 3 H), 4.6 (d, 1 H, J = 5.5), 5.47 (dd, 1 H, J = 5.9, 2.7), 5.77 (dm, 1 H, J = 9.3, 2.7), 6.17 (m, 1 H), 6.95−7.82 (8 H); ^{13}C NMR (50 MHz) δ 21.4, 30.9, 56.8, 61.7, 75.7, 98.0. **20**: IR 1600, 1558, 1362, 1170 cm^{-1}; ^1H NMR (200 MHz) δ 2.26 (s, 3 H), 2.45−2.55 (dm, 1 H, J = 16.9), 2.78−2.90 (ddd, 1 H, J = 16.9, 6.3, 2.2), 3.44 (s, 3 H), 4.0 (dd, 1 H, J = 4.0, 2.4), 4.17 (dd, 1 H, J = 6.0, 2.1), 5.61 (dm, 1 H, J = 9.1, 2.9), 5.82 (m, 1 H), 6.90−7.60 (8 H); ^{13}C NMR (50 MHz) δ 21.3, 30.5, 58.4, 69.2, 82.7, 82.8, 115.3, 124.1, 126.3, 127.2, 127.5, 129.3, 129.6, 130.0, 133.1, 133.6, 143.4, 143.9. Selected data for **21**: IR 1382, 1178 cm^{-1}; ^1H NMR (200 MHz) δ 2.27 (s, 3 H), 3.33 (s, 3 H), 4.75 (dd, 1 H, J = 5.8, 1.9), 5.59 (dd, 1 H, J = 9.6, 2.9), 5.91 (m, 1 H, J = 3.5); ^{13}C NMR (50 MHz) δ 21.5, 31.4, 58.3.

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Supporting Information Available: Main crystallographic parameters for adducts **14b** and **16c**, copies of ^1H NMR and ^{13}C NMR spectra for compounds **12**, **14b**, **16b**, **17b**, **16c**, **17c**, and **20**; ^1H NMR spectra for compounds **14c**:**15**, **16a**:**17a**, **19**:**21,** and **15**; and two-dimensional NMR for **16a**:**17a**, **16c**, **17c**, **19**:**21**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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