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Activation of the Dienophilicity of Indoles in Normal Electron Demand [4 + 2] Cycloadditions under High Pressure

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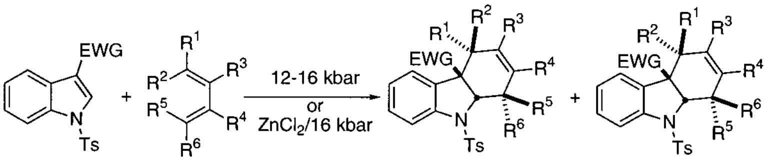
ABSTRACT

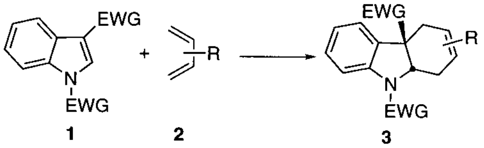


4 **5** **6** **7**

Activation by either high pressure or a combination of Lewis acid catalysis and high pressure allows indole derivatives to behave as dienophiles in [4 + 2] cycloaddition reactions *under mild conditions*. The biactivation mode has the highest impact on the stereoselectivity of the reaction. The cycloadducts resulting from these reactions are characterized by boat-shape conformations that bear well-defined orthogonal planes.

It has been known for some time that indole can react as a dienophile under extreme conditions or in reverse electron demand [4 + 2] cycloaddition processes.[1] The peculiarities of the reaction conditions have, however, long kept those transformations from becoming synthetically useful. More recently, we and others have shown that indole, when properly substituted, can act as dienophile in *normal* electron demand [$4\pi + 2\pi$] cycloaddition reactions.[2] Thus indoles bearing an electron-withdrawing group (EWG) in position 3 and a sulfonyl or acyl substituent in position 1 show a dienophilic behavior toward electron-rich dienes and give the expected cycloadducts (of the type **3**) in fair to excellent yields (Scheme 1).

Scheme 1



1 **2** **3**

When the electron-withdrawing group placed in position 3 of the indole is a carbon-centered function such as carboxaldehyde or ester, for example, the process leads to an irreversible dearomatization of the five-membered ring

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(1) (a) Takahashi, T.; Ishida, H.; Kohmoto, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1725−1726. (b) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856−867. (c) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610−4614. (d) Bäckwall, J.-E.; Plobeck, N. A. *J. Org. Chem.* **1990**, *55*, 4528−4531. (e) Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405−1411. (f) Markgraf, J. H.; Patterson, D. E. *J. Heterocycl. Chem.* **1996**, *33*, 109−111. (g) Haberl, U.; Steckhan, E.; Blechert, S.; Wiest, O. *Chem. Eur. J.* **1999**, *5*, 2859−2865. (h) Hsieh, M.-F.; Rao, P. D.; Liao, C. C. *Chem. Commun.* **1999**, 1441−1442.

(2) (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188−7194. (b) Kraus, G. A.; Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605−5608. (c) Kraus, G. A.; Bougie, D. *J. Org. Chem.* **1989**, *55*, 2425−2428.

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Table 1. Reactions between Indole **4** and Dienes **5** under Thermal, Lewis Acid Catalysis, and/or High Pressure Activation

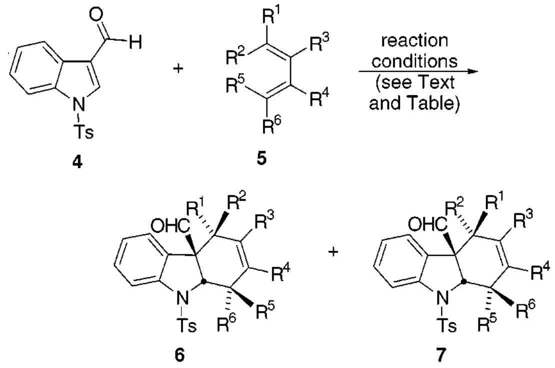
entry	diene	temp (°C)	reaction time (h)	pressure (kbar)	Lewis acid	% conversion	yields **6** + **7** (%)[a]	*endo*/*exo* (**6**/**7**) ratio
1	**5a**	200	72			67	60	
2	**5a**	200	216			85	71	
3	**5a**	60	96	12		65	nd[b]	
4	**5a**	50	48	16		93	46	
5	**5a**	**25**	**24**	**16**	**$ZnCl_2$**	**96**	**46**	
6	**5b**	195	72			25	25	80:20
7	**5b**	45	144	12		30	nd[b]	93:7
8	**5b**	50	48	16		86	50	96:4
9	**5b**	70	120		$ZnCl_2$	61	48	96:4
10	**5b**	**25**	**48**	**16**	**$ZnCl_2$**	**100**	**62**	**>98:2**
11	**5c**	195	72			100	57[c]	75:25
12	**5c**	**45**	**96**	**12**		**100**	**92[c]**	**80:20**
13	**5c**	110	24		$ZnCl_2$	80	*d*	
14	**5c**	25	24	16	$ZnCl_2$	100	dec[e]	

[a] We often noted the formation of polymeric materials, which sometimes render isolation of the products difficult. [b] Not determined [c] Isolated in the form of the ketone resulting from hydrolysis of the silyl enol ether group. [d] Cycloadduct **8** was isolated in a 52% yield after hydrolysis of the silyl enol ether group. [e] The formation of a complex mixture of unidentified products together with minor amounts of cycloadduct **8** was observed.

and to a product possessing a quaternary carbon at the ring junction. The structures thereby produced and the stereochemistry characterizing the newly created stereocenters point the finger at possible applications in the realm of indole-based alkaloids. Nevertheless and despite the yields, the conditions of high temperature (typically 195−270 °C) and long periods of time (48−72 h) necessary for the reactions to occur have kept the methodology from being applicable on sensitive substrates and in total synthesis of natural and unnatural products. In addition, low conversions were reported in several cases. We have thus undertaken a study to determine more friendly conditions for these transformations, and we now report that activation by either Lewis acid catalysis or hyperbar activation, or both, allows those reactions to proceed satisfactorily under much milder conditions.

Heating 1-*p*-toluenesulfonylindole 3-carboxaldehyde (**4**) with 2,3-dimethyl-1,3-butadiene (**5a**), 1,3-cyclohexadiene (**5b**), or the electron-enriched 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene, **5c**) under the published conditions (195 °C, 72 h, sealed tubes) led to conversions of 67%, 25%, and 100%, respectively (Scheme 2) (Table 1, entries 1, 6, and 11).[2a] These conversions could be translated into isolated yields of 60%, 25%, and 57%, respectively. Increasing the reaction time from 72 to 216 h in the case of diene (**5a**) led to a better conversion (82%) and isolated yield (71%) (Table 1, entry 2). However, the excessive time required (9 days), as well as the harsh reaction conditions, clearly detract from the attractiveness of the procedure.

Scheme 2



a : R^1=R^2=R^5=R^6=H ; R^3=R^4=CH_3
b: R^1=R^3=R^4=R^6=H ; R^2,R^5 = -$(CH_2)_2$-
c : R^2=R^3=R^5=R^6=H ; R^1=OCH_3 ; R^4=$OSi(CH_3)_3$

Acceleration of the Cycloaddtion Process. Research from the past decades has shown that pressure in the range of 1−20 kbar strongly influences the rate of processes accompanied by a decrease in volume. The highly negative activation volumes (typically −23 to −51 cm^3 mol^{-1}) characterizing the Diels−Alder cycloadditions have generated many studies that unambiguously demonstrate a powerful pressure-induced acceleration of these organochemical transformations.[3] When a mixture of indole **4** and dimethylbutadiene **5a** in methylene chloride was compressed to 12 kbar for 96 h at 60 °C, a conversion of 65% was obtained (Table 1, entry 3). Increasing the pressure to 16 kbar led to an almost quantitative conversion after only 48 h (entry 4). Similarly, 1,3-cyclohexadiene (**5b**) under essentially identical conditions led to conversions of 30% (12 kbar) and 86% (16 kbar) (entries 7 and 8). In the case of the more reactive diene **5c**, however, a quantitative conversion was already observed at 12 kbar and 45 °C, the result of the activation of the dienic component by the two ether groups (entry 12).

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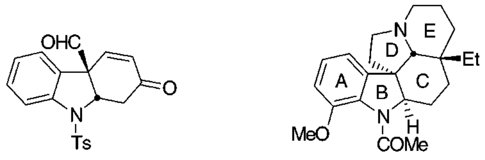
(3) (a) Isaacs, N. *Tetrahedron* **1991**, *47*, 8463−8497. (b) Klaerner, F.-G., Diedrich, M. K.; Wigger, A. E. In *Chemistry under Extreme or Non-Classical Conditions*; Van Eldick, R., Hubbard, C. D., Eds; John Wiley and Sons: New York, 1997; pp 103−161. (d) Jurczak, J.; Gryko, D. T. In *Chemistry under Extreme or Non-Classical Conditions*; Van Eldick, R., Hubbard, C. D.; John Wiley and Sons: New York, 1997; pp 163−188.

Several examples of chemical transformations (including cycloaddition reactions) involving successful *multiactivation* based on both pressure and Lewis acid catalysis have also been reported in the literature.[4] A recent study demonstrated the absence of modification of activation volumes in the presence of those catalysts.[5] Entries 5 and 10 of Table 1 depict the results obtained when zinc chloride (10% mole equiv) was added in the medium before applying pressure. In the case of 2,3-dimethyl-1,3-butadiene (**5a**), the reaction temperature was decreased to 25 °C and the time was reduced to 24 h to achieve an essentially identical result (entry 5). A similar behavior was observed with cyclohexadiene **5b** (entry 10). Danishefsky's diene **5c** afforded an untractable mixture of products, presumably resulting from the destruction of the more sensitive diene under those conditions. For comparison purposes, the cycloaddition reactions between indole **4** and dienes **5b** and **5c** were also carried out by using zinc chloride activation alone (entries 9 and 13, respectively). Thus heating **4** and **5b** in the presence of $ZnCl_2$ (10% mole equiv) at 70 °C for 120 h led to a conversion of 83%. Similarly an 80% conversion was observed for **5c** under analogous conditions and led to a new cycloadduct **8** (Figure 1) whose structure analysis revealed the loss of methanol. It is of interest to note that activation by high pressure alone furnishes in this case the original cycloadducts **6c** and **7c** (i.e., having kept the methoxy substituent) in nearly quantitative yield (entry 12).[6]



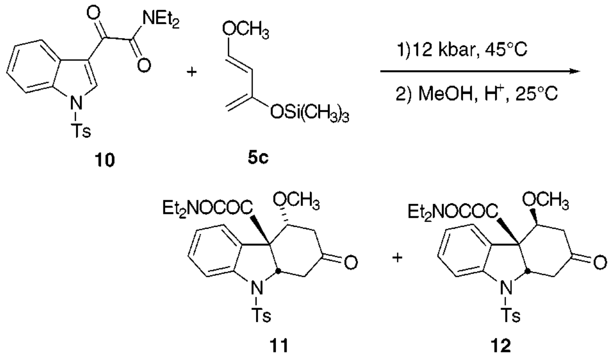
8 **9**

Figure 1.

Comparing entries 11 and 12 clearly indicates the advantages of high pressure alone, while the combination of high pressure and Lewis acid catalysis is best illustrated by entries 4 and 5, as well as 8 and 10.

Indole **10**, featuring a ketoamide group in position 3, was chosen as a more reactive substrate possessing the number of atoms (C−C−N) necessary for the building of the D ring of the *Aspidosperma* alkaloids skeleton (see for instance aspidospermine (**9**), Figure 1).[7] When a methylene chloride solution of glyoxamide **10** and Danishefsky's diene **5c** was placed under 12 kbar and at 45 °C for 48 h, a complete conversion was observed, and after hydrolysis of the silyl enol ether function, a 3:1 mixture of *endo*/*exo* cycloadducts **11** and **12** was obtained (Scheme 3). Separation by chromatography on silica led to an isolated yield of 60% (**11** + **12**), and careful crystallization of the major isomer in a mixture of heptane and ethyl acetate furnished a material suitable for X-ray diffraction analysis (vide infra).

Scheme 3



Stereochemical Implications. The impact of the mono- and biactivation modes described here on the stereoselectivity of the reaction can be evaluated by the results depicted in entries 6−10 of Table 1. Thus the thermal reaction between indole **4** and cyclohexadiene **5b** led to the formation of a 4:1 mixture of *endo* and *exo* cycloadducts **6b** and **7b**.[8] Compressing the substrates to 12 kbar increased this ratio to 93:7, while a pressure of 16 kbar further improved it to 96:4. The same values were observed when the reaction was activated by zinc chloride alone at 70 °C. Biactivation by pressure and the same Lewis acid gave the best result (>98:2), the *exo* stereoisomer being undetectable by ^1H NMR spectrometry analysis. It is worthwile to note that high pressure furnished only a slight improvement of the *endo*/*exo* isomers ratio in the case of diene **5c**.

Determination of Stereoisomeric Structures. Analysis of ^1H NMR data clearly indicates these cycloadducts to result from a preferential *endo* approach. This has been undoubtedly assessed in one case by single-crystal X-ray diffraction. The solid-state conformation of one enantiomer of **11** is depicted in Figure 2; its cyclohexanone moiety appears to be of the concave boat-shape type.

This topology is likely to be conserved in solution, since the dihedral angles observed on the crystal structure are in fine agreement with those deduced from the $^1H-^1H$ coupling constants measured by ^1H NMR spectrometry. Determination of the coupling constants of the minor isomer indicates it adopts a similar boat-shape concave conformation. Albeit such boatlike topologies may seem unusual at first, there exists a few precedents in the literature.[9] In particular the conformational rigidity imposed by the chiral tricyclic system

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(4) (a) Aben, R. W.; Limburg, E. P.; Scheeren, H. W. *High Press. Res.* **1992**, *11*, 167−170. (b) Dauben, W. G.; Hendricks, R. T. *Tetrahedron Lett.* **1992**, *33*, 603−606. (c) Choi, M. C.; Chen, S. S.; Matsumoto, K. *Tetrahedron Lett.* **1997**, *38*, 6669−6672.

(5) Jenner G. *New J. Chem.* **1997**, *21*, 1085−1090.

(6) The adducts were isolated in the form of the ketones resulting from hydrolysis of the corresponding silyl enol ethers.

(7) Southon, I. W.; Buckingham, J. *Dictionary of Alkaloids*; CRC Press: London, 1989; pp 103−161.

(8) *Endo* addition can be defined as "that particular spatial arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile", meaning the indole part in this case. See: Fringuelli, F.; Taticchi, A. In *Dienes in the Diels−Alder Reaction*; John Wiley and Sons Ltd: New York, 1990; pp 1−44.

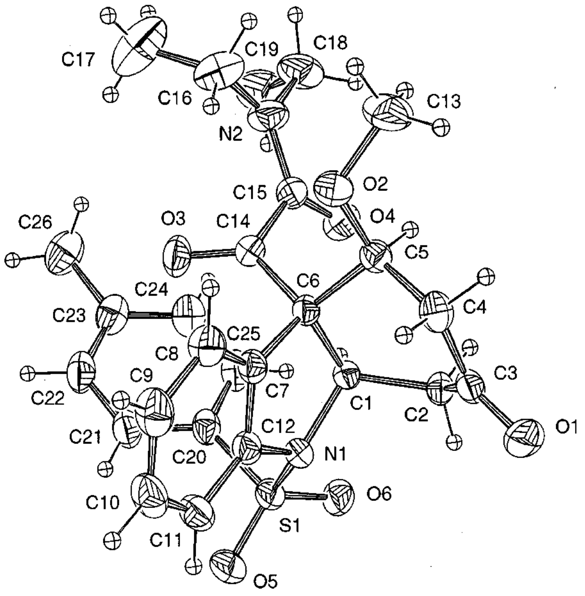

Figure 2.

of **11** bears well-defined perpendicular planes, and this feature may be the starting point for the development of new ligands for asymmetric catalysis.[10]

Conclusion. The results described in this paper show that activation by either high pressure or a combination of high pressure and Lewis acid catalysis allows indole derivatives to behave as dienophile in [4 +2] cycloaddition reactions *under mild conditions*. High pressure or Lewis acid catalysis increase the *endo*/*exo* ratio of diastereomeric cycloadducts; however, the best result is observed when the biactivation mode is applied to the reaction. Further work is in progress to apply these conditions to substrates leading to intermediates en route to the preparation of natural alkaloids. Moreover, the concave boat-shape conformations characterizing the cycloadducts bear well-defined perpendicular planes, and this interesting feature may be exploited in the future for the design and preparation of new ligands useful in the context of asymmetric catalysis.

Supporting Information Available: Experimental procedure and complete characterization for compounds **6a**, **6b**, **7b** the ketones obtained from hydrolysis of cycloadducts **6c** and **7c**, **8**, **11** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001−7008. (b) Maddaluno, J.; Gaonac'h, O.; Marcual, A.; Toupet, L.; Giesner-Prettre, C. *J. Org. Chem.* **1996**, *61*, 5290−5306.

(10) See for instance: (a) *Acc. Chem. Res.* **2000**, *33*, 324−440 (special issue on catalytic asymmetric synthesis). (b) Wills, M.; Tye, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1109−1132.