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Normal electron demand Diels–Alder cycloaddition of indoles to 2,3-dimethyl-1,3-butadiene

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Dedicated to the memory of Professor Rafael Suau of the University of Málaga, who died on November 11th 2010

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ABSTRACT

The influence of experimental conditions and of a wide range of electron-withdrawing indole substituents has been studied in the thermally activated and Lewis acid activated intermolecular Diels–Alder cycloaddition of electron-poor indoles to 2,3-dimethyl-1,3-butadiene.

1. Introduction

Indoles generally behave as electron-rich dienophiles in inverse Diels–Alder (DA) reactions with electron-poor dienes such as tetrazine derivatives,[1] the cycloaddition being controlled by interaction between the indole HOMO and the diene LUMO. However, indoles in which the nitrogen and C3 atoms bear electron-withdrawing groups (EWGs) can also take part in normal electron demand Diels-Alder reactions (DAs), the EWGs narrowing the energy gap between the indole LUMO and the diene HOMO.[2,3] For these latter reactions it is usually necessary to employ very high temperatures (150–270 °C) and long reaction times (1–4 days),[4] although the negative activation volumes of DAs has been exploited by using pressure[5] to allow the use of lower temperatures (11.5–16 kbar, 25–50 °C), sometimes in combination with a Lewis acid catalyst.[6] A few low-temperature normal electron demand DAs of indoles have also been achieved by means of photocatalysis,[7] microwaves,[8] or ambient-pressure Lewis acid catalysis.[9] A nitro group as C3 EWG is lost as nitrous acid during the reaction, but carbon-centred EWGs result in the quaternary carbon often found in indole alkaloids. Our interest in a quick route to the carbazole unit of these alkaloids has led us to carry out an extensive study of the effects of experimental conditions and EWGs on the yield of the DA reactions of indoles.

2. Results and discussion

2.1. Evaluation of experimental conditions

Taking the intermolecular DA reaction of 3-acetyl-1-tosylindole (**1a**) with 2,3-dimethyl-1,3-butadiene as a model (Scheme 1) we first study the effects of solvent, dienophile/diene ratio, temperature and additives.

Heating **1a** in a sealed tube with 12 equiv of diene in toluene at 250 °C afforded only 20% conversion after 72 h (Table 1, entry 1). Doubling the amount of diene gave slightly improved conversion at lower temperature (30%, 150 °C; entry 2), or 85% conversion after 168 h at 250 °C (entry 3). With 36 equiv of diene, heating for 96 h at 250 °C achieved complete conversion and a 79% yield of the chromatographically purified adduct **2a** (entry 4). Attempts to activate the dienophile[10] with the Lewis acids boron trifluoride and zinc chloride failed to allow the use of lower temperatures (entries 5 and 6), but the joint use of *N*,*N*,*N*′,*N*′-tetramethylnaphthalene-1,8-

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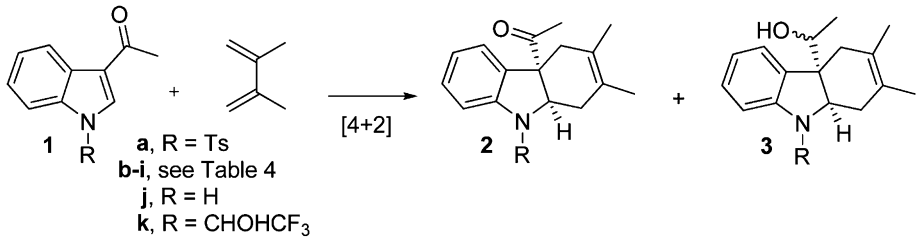


Scheme 1. Diels–Alder reaction of indoles **1** with 2,3-dimethylbuta-1,3-diene.

diamine (proton sponge) and 2,4,6-tri-*tert*-butylphenol (BHT)[11] allowed an 85% yield of purified **2a** to be obtained under the same temperature and time conditions as in entry 4 but with three times less diene (entry 7).

Table 1
DA reaction of indole **1a** with 2,3-dimethylbuta-1,3-diene in toluene[a]

Entry	Diene (equiv)	*T*/°C	*t*/h	Additive (equiv)	% Conv.	**2a** (% yield)[b]
1	12	250	72	—	20	12
2	24	150	120	—	30	20
3	24	250	168	—	85	68
4	36	250	96	—	100	79
5	12	50	15	$BF_3{\cdot}OEt_2$ (5)	0	—
6	12	100	72	$ZnCl_2$ (0.2)	20	6
7	12	250	96	Proton sponge (1), BHT (1)	95	85

[a] Conditions: indole **1a** (0.064 mmol), toluene (0.3 mL).
[b] Yield after chromatographic purification.

As usual with DA reactions, replacing the organic solvent with water increased the reaction rate (Table 2, entry 1; cf. Table 1, entry 2); this is attributed to hydrophobic packing of diene and dienophile, aggregation processes and the high internal pressure of water.[12,13] Conversion and yield were increased by increasing the temperature and reaction time (entries 2 and 3), but returned to entry 1 levels upon inclusion of *iso*-propanol as co-solvent (entry 4).[14] Addition of β-cyclodextrin [15] or $In(OTf)_3$[16] failed to allow reaction at 100 °C (entries 5 and 6), and addition of LiCl[17] or $CaCl_2$[18] (entries 7 and 8) did not improve the results of entry 2 after 96 h at 250 °C. Thus in both water and toluene, yields in excess of 75% required prolonged heating at high temperature, though the addition of proton sponge and BHT allows the use of a larger dienophile/diene ratio in toluene.

Table 2
DA reaction of indole **1a** with 2,3-dimethylbuta-1,3-diene in H_2O[a]

Entry	*T*/°C	*t*/h	Additive (equiv)	% Conv.	**2a** (% yield)[b]
1	150	120	—	60	45[c]
2	250	96	—	93	84
3	250	144	—	100	90
4	250	144	—	65	52[d]
5	100	96	β-Cyclodextrin (1.6)	0	—
6	100	96	$In(OTf)_3$ (1)	0	—
7	250	96	LiCl (22)	35	28
8	250	96	$CaCl_2$ (10)	80	60

[a] Conditions: indole **1a** (0.064 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), H_2O (0.3 mL).
[b] Yield after chromatographic purification.
[c] With 12 equiv of diene.
[d] H_2O/*i*-PrOH as co-solvent (0.15:0.15 mL).

As noted in the Introduction, DA reactions are sometimes accelerated, or occur at lower temperatures, in the presence of Lewis acids.[10] In the present study, no cycloaddition of **1a** to dimethylbutadiene occurred in rt methylene chloride in the presence of $AlCl_3$,[3a] $LiClO_4$,[19] CuOTf,[20] or TMSOTf[21] (Table 3, entries 1, 2 and 6–8). $TMSNTf_2$[22] afforded 100% conversion within 1 h, but the yield of **2a** after chromatographic purification was only 32% (entry 9). Mixtures of $TfNH_2$ with Et_2AlCl[23] or Me_3Al with $AlCl_3$[24] gave both lower conversion and lower yield than $TMSNTf_2$ (entries 11 and 12), and the use of $TMSNTf_2$ at 0 °C likewise reduced yield (entry 10). With Et_2AlCl,[9] conversion was poor at −20 °C or after 2 h at rt (entries 3 and 4), and only 70% after 21 h at rt (entry 5), but these last conditions afforded a 48% combined yield of **2a** (4%) and its reduction product[25] **3a** (44%); compound **3a**, obtained as a 17:8 mixture of epimers, was identified by comparison of its NMR spectra with those of a 3:2 epimeric mixture obtained by reduction of ketone **2a** with $NaBH_4$ in MeOH.

Table 3
DA reaction of indole **1a** with 2,3-dimethylbuta-1,3-diene with additives[a]

Entry	*T*/°C	*t*/h	Additive (equiv)	% Conv.	Cycloadduct (% yield)[b]
1	22	17	$AlCl_3$ (5)	0	—
2	22	7	$AlCl_3$ (5)	0	—[c]
3	−20	21	Et_2AlCl (5)	20	—
4	22	2	Et_2AlCl (5)	10	—
5	22	21	Et_2AlCl (5)	70	**2a** (4) **3a** (44)
6	22	72	$LiClO_4$ (10)	0	—[c]
7	22	72	CuOTf (1)	0	—
8	22	26	TMSOTf (2)	0	—
9	22	1	$TMSNTf_2$ (2)	100	**2a** (32)
10	0	4	$TMSNTf_2$ (2)	100	**2a** (20)
11	22	17	$TfNH_2$(2)+Et_2AlCl(4)	85	**2a** (20)
12	22	24	Me_3Al (0.5)+$AlCl_3$(5)	85	**2a** (8)
13	22	43	K-10 (0.5 g/mmol)	0	—[d]
14	22	43	$In(OTf)_3$ (5)	0	—[d]

[a] Conditions: indole **1a** (0.064 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), CH_2Cl_2 (0.3 mL).
[b] Yield after chromatographic purification.
[c] Solvent: CH_2Cl_2/Et_2O (0.5:0.5 mL).
[d] Solvent: 1-ethyl-3-methylimidazolium tetrafluoroborate.

No cycloaddition of **1a** to dimethylbutadiene occurred in the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate in the presence of montmorillonite K-10[26] or $In(OTf)_3$[27] (Table 3, entries 13 and 14).[28]

2.2. Effect of the *N*-substituent

Electron-withdrawing substituents on the indole nitrogen increase the rate of normal electron demand DA reactions under hyperbaric conditions.[6e] In order to evaluate this effect in our model reaction we prepared the series of indoles **1b**–**i**, in which the Ts group on the nitrogen of **1a** has been replaced with one of the EWGs Ns, Ms, Tf, Boc, Ac, Bz, CF_3CO and *p*-NO_2Bz, by reaction of 3-acetylindole with the appropriate *N*-protecting reagent, and were reacted with 24 equiv of dimethylbutadiene either in toluene at 250 °C, or in rt methylene chloride containing Et_2AlCl (Table 4).

Table 4
DA reaction of *N*-substituted indoles **1a**–**i** with 2,3-dimethylbuta-1,3-diene

Entry	indole	R	Thermal[a]			Lewis acid activated[b]			
			t/h	Products (% yield)		*t*/h	Products (% yield)		
1	**1a**	Ts	168	**1a** (15)	**2a** (68)	2	**1a** (95)		
2	**1a**		—	—	—	21		**2a** (4)	**3a** (44)
3	**1b**	Ns	168	Mixture		4	**1j** (100)		
4	**1c**	Ms	156		**2c** (93)	1	**1c** (95)		
5	**1c**		—	—	—	42			**3c** (60)
6	**1d**	Tf	96		**2d** (100)	2		**2d** (31)	**3d** (31)
7	**1d**		—	—	—	42		**2d** (0)	**3d** (51)
8	**1e**	Boc	22	**1j** (100)		2		**2j** (21)	**3j** (43)
9	**1e**		—	—	—	17			**3j** (48)
10	**1f**	Ac	144	**1f** (25)	**2f** (61)	1			**3f** (90)
11	**1g**	Bz	144	**1g** (20)	**2g** (77)	4			**3g** (92)
12	**1h**	CF_3CO	156	**1j** (40)	**2h** (49)	17	**1k** (50)		**3h** (0)
13	**1i**	*p*-NO_2Bz	12	**1i** (30)	**2i** (51)	2			**3i** (0)

[a] Conditions: indole **1a**–**i** (0.1–0.2 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), toluene (0.5 mL/0.1 mmol), 250 °C.
[b] Conditions: indole **1a**–**i** (0.1 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), Et_2AlCl (5 equiv), CH_2Cl_2 (0.5 mL), rt.

Under thermal conditions in toluene the Ms and Tf derivatives both afforded significantly larger yields than did **1a** (Table 4, entries 1, 4 and 6); in particular, the Tf derivative **1d** afforded a quantitative yield of **2d** within a relatively short time (96 h). The Boc derivative **1e** underwent thermolysis to the deprotected ethanone **1j** before it could react with dimethylbutadiene (entry 8), as did 40% of the CF_3CO derivative **1h** (entry 12). Other carbon-centred EWGs (Ac, Bz) afforded results similar to those of Ts (entries 1, 10, 11), but the 4-nitrobenzamide group of **1i** facilitated 70% conversion within 12 h, with a 51% yield of **2i** and 30% recovery of the starting indole (entry 13).[29]

In rt methylene chloride containing 5 equiv of Et_2AlCl, no cycloadducts were obtained from **1b**, **1h** or **1i**; the nosyl group of **1b** was labile, the trifluoroacetyl group of **1h** underwent reduction, and **1i** was unstable (entries 3, 12, 13). Compound **1c** gave a somewhat greater yield than **1a**, but in twice the time (entries 2 and 5). The stronger EWG Tf afforded a 62% combined yield of cycloadducts **2d** and **3d** in only 2 h (entry 6), and Boc a 64% combined yield of the deprotected adducts **2j** and **3j**, though **2j** disappeared upon prolonged stirring (entries 8 and 9). Best results were obtained with Ac and Bz, which afforded the reduced cycloadduct in yields of 90% or more after 17 and 4 h, respectively (entries 10 and 11). That these acyl groups performed better than the sulfonyl groups is attributable to their achieving greater delocalization of the nitrogen lone pair and hence greater de-aromatization of the pyrrole ring,[6e] thus making differences in dienophilic character that are better expressed in these experiments at rt than in the high temperature experiments.

Progressive reduction of the amount of Et_2AlCl to 1 equiv lowered the yield progressively (Table 5, entries 2 and 3) unless a longer reaction time was employed (entry 4); with 0.1 equiv, no conversion had occurred even after 24 h (entry 5).

Table 5
Effect of the amount of Et_2AlCl in the DA reaction of **1f** and 2,3-dimethylbuta-1,3-diene[a]

Entry	Et_2AlCl (equiv)	*t*/h	Products (% yield)	
1	5	1		**3f** (90)
2	2.5	1		**3f** (75)
3	1	1	**1f** (50)	**3f** (14)
4	1	23		**3f** (80)
5	0.1	24	**1f** (100)	

[a] Conditions: indole **1f** (0.1 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), Et_2AlCl, CH_2Cl_2 (0.5 mL), rt.

2.3. Effect of the C3 substituent

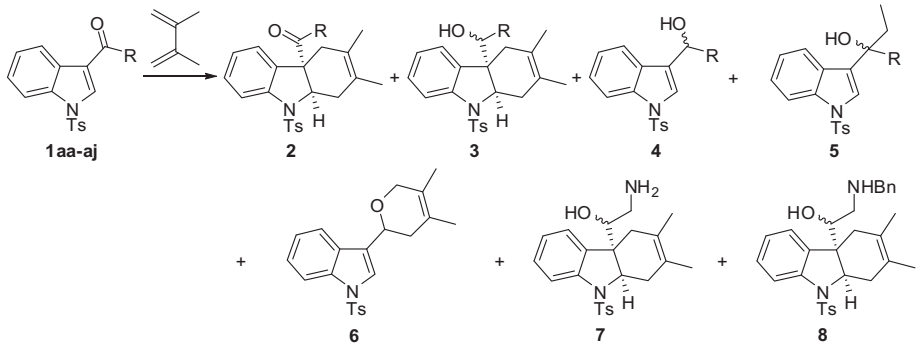
In evaluating the effect of the C3 substituent we were especially interested in tryptamine-like indoles providing cycloadducts of use for construction of the tetracyclic 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole skeleton of many indole alkaloids. With Ts on the indole nitrogen, good yields were obtained under thermal conditions with formyl and ketoester C3 substituents (Table 6, entries 1 and 3), and also for the tryptamine-like compounds **1ah** and **1ai**, in which a secondary exocyclic amine is protected with Cbz (entries 8–11; note the beneficial effects of using water as solvent or adding proton sponge and BHT). Amides (entries 4 and 5), Boc-protected amines (entries 6 and 7) and tertiary amines (entry 12) reacted sluggishly and afforded only complex mixtures of products.

In rt methylene chloride containing Et_2AlCl, yields were generally no better than 30–40%, and the major product was often not the desired cycloadduct. Thus the formyl derivative **1aa** afforded mainly dihydropyran **6**, the result of a hetero Diels–Alder cyclization (entry 1); while ketoester **1ac** and ketoamide **1ad** suffered reduction of their carbonyl and nucleophilic addition of ethyl, affording mixtures of the corresponding derivatives of types **4** and **5** (entries 3 and 4). The Cbz-protected tryptamine-like compound **1ai** did undergo cyclization (albeit with reduction of the carbonyl), but only after 20 h and in very low yield (entry 11). Most of the indoles that had performed worst under thermal conditions behaved better when activated by Et_2AlCl, but not well enough, the best result being the 45% combined yield of reduced and unreduced cycloadduct obtained from the tertiary ketoamide **1ae** (entry 5). Compound **1aj** afforded only a 32% yield of **2aj** after 41 h (albeit with recovery of 17% of the starting tosylamide; entry 12); while the Boc-protected tryptamine-like compounds **1af** and **1ag** gave, respectively, 24% and 31% yields of cycloadducts with reduced carbonyls and deprotected amines (entries 6 and 7).

Finally, we evaluated a few combinations of *N*- and C3-substituents. Under thermal conditions, the *N*-substituent Tf and the C3 substituent $CH_2NMeCbz$, both of which had performed well individually under these conditions, behaved synergically, affording a 94% yield of cycloadduct **2dh** after only 48 h (Table 7, entry 1; cf. entry 6 of Table 4 and entry 8 of Table 6). By contrast, the combination of $CH_2NMeCbz$ with the *N*-substituent *p*-NO_2Bz, with which promising results had been obtained under thermal conditions (Table 4, entry13), produced only a complex mixture after 48 h of reaction (Table 7, entry 5). Also, in the presence of Et_2AlCl the combination of the *N*-substituent Ac and the C3-substituent CH_2NBn_2, both of which had afforded near-best results with this Lewis acid, behaved very irregularly (entries 3 and 4); and an attempt to improve the performance of **1e** under Lewis acid activation by placing a $CH_2NHCOCF_3$ group at C3 halved the yield of cycloadduct, with loss of the Boc group (entry 2).

In conclusion, we have studied Diels–Alder cycloaddition of electron-poor indoles to 2,3-dimethyl-1,3-butadiene both at high temperature and under activation by Lewis acids at rt. Under thermal conditions the reaction is accelerated by increasing the temperature, increasing the amount of diene, adding proton sponge and BHT and carrying out the reaction in water rather than toluene; for 3-acetylindoles, the best *N*-substituents are Ms and Tf. Activation by Lewis acids at rt reduces the reaction time to a few hours, but affords lower isolated yields; best results are obtained with Et_2AlCl (although the carbonyl of an acyl C3 substituent is in this case generally reduced), and for 3-acetylindoles, the best *N*-substituents are Ac and Bz. Among tryptamine-like derivatives with 2-aminoethanoyl C3 substituents, best results are obtained with Tf on the indole nitrogen and the side chain nitrogen protected as a tertiary Cbz carbamate; under thermal conditions, this combination affords a high yield of cycloadduct in only 48 h.

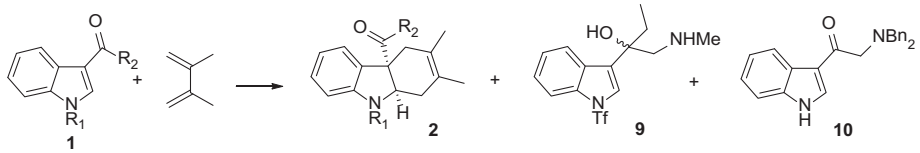
Table 6
Effect of the C3 substituent in DA reaction of tosyl indoles



Entry	Indole	R	Thermal[a]		Lewis acid activated[b]			
			t/h	Products (% yield)	*t*/h	Products (% yield)		
1	**1aa**	H	72	**2aa** (79)[6d]	2		**3aa** (11)	**6** (29)
2	**1ab**	CO_2H	72	Mixture	2	Mixture		
3	**1ac**	CO_2Me	144	**2ac** (90)[6d]	2		**4ac** (20), **5ac** (55)	
4	**1ad**	CONHBn	73	Mixture	2		**4ad** (20), **5ad** (47)	
5	**1ae**	CH_2NBnAc	96	Mixture	48	**2ae** (26)	**3ae** (19)	
6	**1af**	CH_2NHBoc	48	Mixture	3			**7** (31)
7	**1ag**	$CH_2NBnBoc$	48	Mixture	3			**8** (24)
8	**1ah**	$CH_2NMeCbz$	144	**2ah** (74)	—			
9	**1ah**	$CH_2NMeCbz$	96	**2ah** (79)[c]	—			
10	**1ah**	$CH_2NMeCbz$	96	**2ah** (77)[d]	—			
11	**1ai**	$CH_2NBnCbz$	168	**2ai** (81)	20		**3ai** (13)	
12	**1aj**	CH_2NBn_2	120	Mixture	41	**2aj** (32)		**1aj** (17)

[a] Conditions: indole **1aa**–**aj** (0.1–0.45 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), toluene (0.5 mL/0.1 mmol), 250 °C.
[b] Conditions: indole **1aa**–**aj** (0.1 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), Et_2AlCl (5 equiv), CH_2Cl_2 (0.5 mL), rt.
[c] Solvent: H_2O.
[d] Additives: proton sponge (1 equiv), BHT (1 equiv).

Table 7
DA reaction of 1,3-disubstituted indoles and 2,3-dimethylbuta-1,3-diene



entry	Indole	R_1	R_2	Thermal[a]		Lewis acid activated[b]		
				t/h	Products (% yield)	*t*/h	Products (% yield)	
1	**1dh**	Tf	$CH_2NMeCbz$	48	**2dh** (94)	2		**9** (39)
2	**1ek**	Boc	$CH_2NHCOCF_3$	—		2	**2el** (34)[c]	
3	**1fj**	Ac	CH_2NBn_2	—		1	**1fj** (51)	**10** (26)
4	**1fj**			—		23	**2fj** (17)	**10** (12)
5	**1ih**	*p*-NO_2Bz	$CH_2NMeCbz$	48	Mixture	—		

[a] Conditions: indole **1** (0.1–0.45 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), toluene (0.5 mL/0.1 mmol), 250 °C.
[b] Conditions: indole **1** (0.1 mmol), 2,3-dimethylbuta-1,3-diene (24 equiv), Et_2AlCl (5 equiv), CH_2Cl_2 (0.5 mL), rt.
[c] Compound **2el**: R_1=Boc, R_2=CH_2NH_2.

3. Experimental

3.1. General procedures

NMR spectra were recorded in $CDCl_3$ at 250.13, 399.97 or 500.13 MHz for ^1H and at 62.83, 100.58 or 125.75 MHz for ^{13}C, using TMS as internal reference. All air-sensitive reactions were run under dried deoxygenated argon, in oven dried glassware, with magnetic stirring; reagents were added by syringe through septa. All solvents for air or moisture-sensitive reactions were dried by standard procedures. All new compounds were chromatographically pure and both identity and homogeneity were provided by HRMS and by ^1H and ^{13}C NMR spectroscopy.

3.2. Typical procedure for thermal DA reactions

*3.2.1. In toluene: cis-1-{2,3-dimethyl-9-[(4-methylphenyl)sulfonyl]-1,4,9,9a-tetrahydro-4aH-carbazol-4a-yl}ethanone (**2a**).* A solution of **1a** (20 mg, 0.064 mmol) and 2,3-dimethyl-1,3-butadiene (177 μL, 1.53 mmol) in dry toluene (0.3 mL) was placed in a 5 mL medium wall glass Schlenk tube with a PTFE stopcock and a 14/23 tapered ground joint at the sidearm. This mixture was heated under Ar for 96 h at 250 °C in a sand bath. *Caution!: A glass tube reactor might explode under excessive internal pressure, so a blast screen must be placed in front of the apparatus to protect the user and the glass sash of the fume cupboard*. After cooling to rt, the solution was concentrated under reduced pressure and the residue was subjected to

flash chromatography (SiO_2, 1:9 EtOAc/hexane), affording cycloaduct **2a** (20 mg, 79%): mp 120 °C. ^{1}H NMR ($CDCl_3$) δ 7.71–7.65 (m, 3H), 7.28–7.25 (m, 1H), 7.20 (d, J=7.9 Hz, 2H), 7.05–7.00 (m, 2H), 4.55 (t, J=5.3 Hz, 1H), 2.60–2.45 (m, 2H), 2.58 (d, J=14.4 Hz, 1H), 2.34 (s, 3H), 2.17 (d, J=14.4 Hz, 1H), 1.71 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 206.5 (CO), 144.2 (C), 142.9 (C), 134.5 (C), 133.7 (C), 129.6 (2×CH), 129.0 (CH), 127.3 (2×CH), 127.2 (C), 126.4 (C), 124.2 (CH), 124.1 (CH), 115.5 (CH), 65.5 (CH), 63.2 (C), 37.4 (2×CH_2), 25.5 (CH_3), 21.5 (CH_3), 19.1 (CH_3), 19.0 (CH_3). IR (KBr) 1707, 1671, 1596, 1477, 1459, 1357 cm^{-1}. MS (EI) (m/z): 395 (M^+, 4), 352 (34), 196 (53), 155 (21), 91 (100). HRMS (EI) calcd for $C_{23}H_{25}NO_3S$: 395.1555, found: 395.1559.

3.2.2. In water. A mixture of **1a** (20 mg, 0.064 mmol) and 2,3-dimethyl-1,3-butadiene (177 μL, 1.53 mmol) in deionized water (0.3 mL) was heated under Ar in a sealed tube at 250 °C in a sand bath for 144 h. After cooling to rt the mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3×10 mL), dried with anhydrous Na_2SO_4 and filtered, and the solvent was evaporated. Purification by flash chromatography (SiO_2, 1:9 EtOAc/hexane) afforded cycloadduct **2a** (22.6 mg, 90%).

3.3. Typical procedure for DA reactions at rt

*3.3.1. cis-1-{2,3-Dimethyl-9-[(4-methylphenyl)sulfonyl]-1,4,9,9a-tetrahydro-4aH-carbazol-4a-yl}ethanol (**3a**).* A 1 M hexane solution of Et_2AlCl (319 μL, 0.32 mmol) was added dropwise to a stirred solution of **1a** (20 mg, 0.064 mmol) and 2,3-dimethyl-1,3-butadiene (177 μL, 1.53 mmol) in CH_2Cl_2 (0.5 mL) and the mixture was stirred at rt for 21 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3×10 mL), dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent, purification by flash chromatography (SiO_2, 1:9 EtOAc/hexane) afforded **3a** (11 mg, 44%) as an oil containing a 3:2 mixture of diastereomers. ^{1}H NMR($CDCl_3$) δ 7.71–7.64 (m, 2.4H), 7.57 (d, J=8.1 Hz, 0.6H), 7.19 (d, J=8.1 Hz, 2H), 7.15–7.14 (m, 1H), 7.09–6.93 (m, 2H), 4.29 (t, J=4.9 Hz, 0.6H), 4.19 (t, J=5.1 Hz, 0.4H), 3.45–3.42 (m, 0.6H), 3.22–3.17 (m, 0.4H), 2.66–2.56 (m, 1H), 2.40–2.34 (m, 1.4H), 2.34 (s, 3H), 2.26 (d, J=14.4 Hz, 0.6H), 2.11 (d, J=14.4 Hz, 0.6H), 2.06 (d, J=12.8 Hz, 0.4H), 1.70 (s, 3H), 1.59 (s, 1.2H), 1.49 (s, 1.8H), 0.82 (d, J=6.4 Hz, 1.8H), 0.60 (d, J=6.4 Hz, 1.2H). ^{13}C NMR($CDCl_3$) δ 143.9 (C), 143.8 (C), 143.1 (C), 142.6 (C), 135.9 (C), 135.4 (C), 135.1 (C), 135.0 (C), 129.5 (CH), 129.4 (CH), 128.4 (CH), 127.4 (CH), 127.2 (CH), 126.8 (C), 126.4 (C), 126.3 (C), 124.2 (CH), 123.8 (CH), 123.7 (CH), 115.0 (CH), 114.5 (CH), 72.7 (CH), 72.6 (CH), 65.3 (CH), 64.8 (CH), 55.3 (C), 55.0 (C), 37.8 (CH_2), 37.5 (CH_2), 37.2 (CH_2), 37.0 (CH_2), 21.5 (CH_3), 19.3 (CH_3), 19.1 (CH_3), 17.4 (CH_3). IR (CsI) 3542, 1597, 1477, 1458, 1349, 1091 cm^{-1}. MS (EI) (m/z): 397 (M^+, 2), 352 (12), 300 (10), 197 (52), 155 (19), 91 (100). HRMS (EI) calcd for $C_{23}H_{27}NO_3S$: 397.1712, found: 397.1719.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.030. These data include MOL files and InChiKeys of the most important compounds described in this article.

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