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Benzofurans as Efficient Dienophiles in Normal Electron Demand [4 + 2] Cycloadditions

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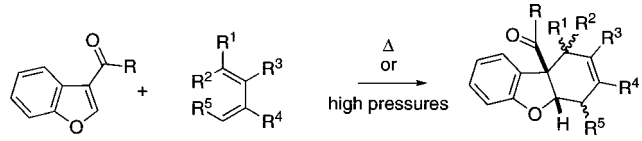

Dearomatization of electron-poor benzofurans is possible through involvement of the aromatic 2,3-carbon−carbon double bond as dienophile in normal electron demand [4 + 2] cycloadditions. The tricyclic heterocycles thereby produced bear a quaternary center at the cis ring junction, a feature of many alkaloids such as morphine, galanthamine, or lunaridine. The products arising from the reaction have been shown to depend on different factors among which the type of the electron-withdrawing substituent of the benzofuran, the nature of the reacting diene, and the method of activation. In the presence of all-carbon dienes, the reaction yields the expected Diels−Alder adducts. When thermal activation is insufficient, a biactivation associating zinc chloride catalysis and high pressure is required to generate the cycloadducts in good yields and high stereoselectivities, for instance, when cyclohexadiene is involved in the process. The use of more functionalized dienes, such as those bearing alkoxy or silyloxy substituents, also shows the limits of the thermal activation, and hyperbaric conditions are, in this case, well-suited. The involvement of Danishefsky's diene induces a competition in the site of reactivity. The aromatic 2,3-carbon−carbon double bond is unambiguously the most reactive dienophile, and the 3-carbonyl unit becomes a competitive site of reactivity with benzofurans bearing substituents prone to heterocycloaddition, in particular under Lewis acid activation. The sequential involvment of both the aromatic double bond and the carbonyl moiety as dienophiles is then possible by using an excess of diene under high-pressure activation. In line with the experimental results, DFT computations suggest that the Diels−Alder process involving the aromatic double bond is preferred over the hetero-Diels−Alder route through an asynchronous concerted transition state. However, Lewis acid catalysis appears to favor the heterocycloaddition pathway through a stepwise mechanism in some cases.

Introduction

The Diels−Alder (DA) cycloaddition represents an efficient tool for the convergent and stereocontrolled synthesis of functionalized polycyclic compounds.[1] The scope of the reaction is large and classically allows the use of five-membered aromatic rings as dienes.[2] Examples of their involvement as dienophiles are more scarce. Benzofurans have been shown, in a few cases, to react as dienophiles in Diels−Alder cycloadditions to generate oxygenated polycycles.[3,4] Because of the high electron density of the aromatic ring, the cycloaddition has been mainly studied with benzo[*b*]furan itself, thus acting as an electron-rich

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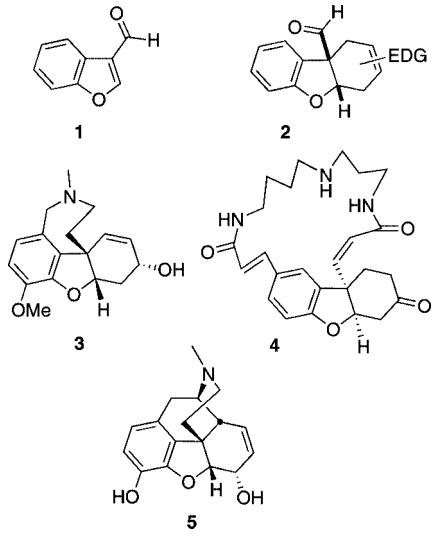

FIGURE 1. Structures of 3-formylbenzofuran **1**, cycloadducts **2**, galanthamine **3**, lunaridine **4**, and morphine **5**.

dienophile in an inverse-electron-demand process.[3] To the best of our knowledge, the only report of its possible involvement in normal demand Diels−Alder cycloadditions was published 20 years ago and describes the reaction between 3-formylbenzofuran **1** and isoprene to deliver cycloadducts **2** as a 2:1 regioisomeric mixture in 67% yield (Figure 1).[4] An interesting feature of this reaction lies in the rapid access to a 6,5,6-tricyclic framework found in many alkaloids (e.g., galanthamine, lunaridine, and morphine for instance). High temperatures (195 °C) were required for the reaction to occur, thus possibly limiting the development of this methodology to nonthermosensitive substrates in the total synthesis of complex molecules. We herein report a study on the scope of substrates and activation methods for these cycloaddition reactions.

Results and Discussion

Four benzofuran derivatives bearing electron-withdrawing groups in position 3 of the heterocycle were singled out.[5] The formyl unit was chosen for the large variety of chemical transformations it allows. The ketoester/ketoamide substituents were also selected as withdrawing groups possessing the number of atoms (C−C−X) necessary for the building of the nitrogenated ring present in many benzofuran-derived alkaloids (Figure 1).

While a variety of synthetic approaches to 3-substituted indoles are available,[6] less attention has been paid to the synthesis of the corresponding benzofurans. A scan of the literature revealed only a few syntheses of such derivatives bearing carbonylated substituents in position 3 of the heteroaromatic. As electrophilic substitutions would lead to the undesired 2-substituted compounds,[7] alternative methods have been developed, mainly based on palladium-catalyzed methods for the construction of the five-membered ring.[8] 2-Substituted benzo[*b*]furans can be prepared by transition-metal-catalyzed coupling of terminal alkynes with *o*-iodophenols, followed by cyclization of the resultant intermediates.[9] However, the use of internal alkynes such as phenylpropiolate, in an attempt to get 3-substituted derivatives, has been shown to furnish a mixture of regioisomers.[10] The problem was circumvented by using silylalkynes to induce a fully regioselective attack and yield the corresponding 2-silylbenzofurans.[10] Bissilylated protected propynol was thus used to synthesize 3-hydroxymethylbenzofuran,[11] which undergoes further oxidation to give 3-formylbenzofuran (**1**).[12] In our hands, however, the four-step sequence furnished the desired compound **1** in only 35% overall yield on a 3 mmol scale, and another synthesis was thus prefered (vide infra).

Carbonylative annulations of *o*-alkynylphenols have been shown to efficiently produce the corresponding 3-aroylbenzofurans but requires the inconvenient use of carbon monoxide.[13] Henke alternatively described the construction of the benzofuran ring via an intramolecular Heck reaction involving a 3-(*o*-bromophenoxy)acrylate.[14] The reaction required large quantities of palladium catalyst (40 mol %) and proved difficult to scale up in our hands. Quite recently, Ma reported the copper-catalyzed formation of 2,3-disubstituted benzofurans from 1-bromo-2-iodobenzenes and β-ketoesters.[15] Hossain also described the synthesis of 3-ethoxycarbonylbenzofurans from an acid-catalyzed reaction between salicaldehydes and ethyldiazoacetate.[16] We selected the method relying on a Heck reaction developed by Ogasawara.[17] This procedure proved easy to scale-up and versatile enough for the synthesis of variously sustituted 3-carbonylated heterocycles **1**, **8**, and **10a**,**b** (Scheme 1).

Coupling 2-iodophenol (**6**) and 2,5-dihydro-2,5-dimethoxyfuran allowed the synthesis of benzofuran **7** and proved efficient on a 10 mmol scale. Benzylic oxidation, using selenium dioxide in dry 1,4-dioxane,[18] furnished the first substrate **8** bearing a ketoester moiety in position 3. Saponification of the ester and transformations of the resulting acid **9** into secondary and tertiary ketoamides **10a** and **10b**, respectively, were achieved in high yields. 3-Formylbenzofuran (**1**) could also be accessed from common intermediate **7** by a two-step sequence involving

(5) The reported higher reactivity of 3-substituted indole derivatives, when compared to 2-substituted ones as electron-poor dienophiles in normal electron demand [$4\pi + 2\pi$] cycloadditions led us to consider the 3-carbonylated benzofurans for this study. See: (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188–7194. (b) Kishbaugh, T. L. S.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 4783–4785.

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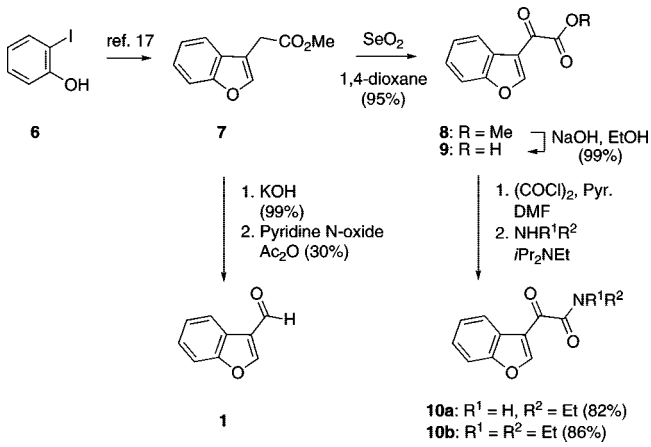
SCHEME 1. Synthesis of 3-Carbonylated Benzofurans 1, 8, and 10a,b



SCHEME 2

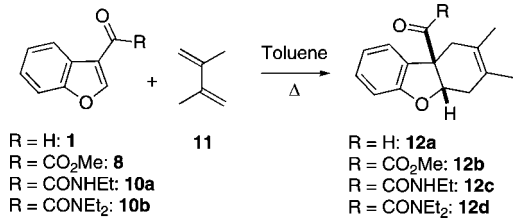


TABLE 1. Reaction with Dimethylbutadiene 11

entry	substrate	*T* (°C)	time (h)	adduct	conv[a] (%)	yield (%)
1	**1**	190[b]	70	**12a**	100	100
2	**8**	180[b]	48	**12b**	100	95
3	**10a**	190[b]	72	**12c**	100	99
4	**10b**	210[b]	60	**12d**	100	98

[a] Conversion. [b] Conducted in a sealed tube.

saponification and subsequent action of pyridine *N*-oxide in acetic anhydride.[19] Alternatively, **1** can be obtained from 3-methylbenzofuran by oxidation using selenium dioxide.[18]

Reacting 3-formylbenzofuran (**1**) with 2,3-dimethylbutadiene (**11**) led to the sole and quantitative formation of the expected tricyclic compound **12a** (Scheme 2; Table 1, entry 1). The reaction required 70 h in toluene to reach completion. Despite its somewhat sluggish character, probably due to the high energy barrier required to dearomatize the five-membered ring, the reaction bears the advantage of stereospecifically assembling a complex tricyclic structure featuring a quaternary center at the ring junction. Similar results were obtained when conducting the cycloadditions with the other 3-substituted benzofuran derivatives (entries 2−4). In all cases, the expected tricyclic compounds were obtained in near-quantitative isolated yields, confirming the reactivity of the aromatic C-2/C-3 double bond of the substituted benzofuran ring as electron-poor dienophile.

We next studied these cycloaddition reactions with cyclohexa-1,3-diene (**13**) (Scheme 3). Interaction of benzofuran **1** with **13** in toluene at high temperature led to the isolation of the expected diastereomeric cycloadducts in 60% yield as a 40/60 mixture of *endo*/*exo* diastereomers **14a** and **15a**.[20] Ketoester **8** proved more reactive and allowed isolation of cycloadducts **14b** and**15b** in a higher 94% yield and a better *endo* selectivity (Table 2, entry 2). Expectedly, the lower electron-withdrawing character of the ketoamide moiety when compared to the ketoester translated into lower isolated yield (entry 3). We previously reported that such cycloadditions involving indoles, pyrroles, and pyridones were strongly accelerated by high pressures and Lewis acid catalysis.[21] Lewis acid catalysis at refluxing toluene led to better yields and *endo*/*exo* diastereoselectivity (entry 4). Compressing benzofuran **10a** and cyclohexadiene **13** to 1.2 GPa did not prove sufficient to promote the cycloaddition reaction in this case (entry 5). In contrast, dual activation by Lewis acid and high pressure led to a complete conversion of the substrates and allowed to isolate cycloadduct **15c** in 79%. These conditions proved also beneficial in increasing the diastereoselectivity of the process to a complete *exo*-selectivity (entry 6). The more sterically hindered tertiary ketoamide derived benzofuran **10b** proved less reactive than the parent secondary ketoamide **10a** (entries 7 and 8) and dual activation also proved beneficial in this case (entry 9).

The involvement of functionalized dienes was also envisaged in the course of this study. In particular, 2-oxygenated dienes were chosen as interesting substrates, allowing the synthesis of cyclohexanone moieties fused to the dihydrobenzofuran ring, a feature found in lunaridine **4**, for instance (Scheme 4). Reacting 3-formylbenzofuran (**1**) in the presence of 2-trimethylsilyloxybutadiene (**16**)[22] at 170 °C, however, resulted in a complete decomposition of the substrates (Table 3, entry 1). The thermal sensitivity of the substrates thus prompted us to try this cycloaddition reaction under high pressure activation. This indeed led to a significant improvement, the starting material being converted to the expected cycloadduct in a 90% ratio. Hydrolysis of the resulting silyl enol ether (vide infra) as well as purification of the tricyclic ketone was tricky in this particular case and led to isolation of **17a** in a disappointing 20% yield (entry 2). Benzofuran **8** proved more robust, and the thermally activated cycloaddition process now led to a complete conversion of the starting material that translated into a good, 83% isolated yield after hydrolysis (entry 3). High pressure activation also proved efficient, giving rise to similar conversion and yields at a much lower reaction temperature (entry 4). Thus, the process expectedly appears to be completely regioselective. In analogy to the behavior of formylated benzofuran **1**, as thermal activation of the cycloaddition with ketoamide-substituted benzofuran **10a** only led to decomposition of the substrate (entry 5). Here again, high-pressure activation proved beneficial, allowing isolation of the expected cycloadduct **17c** in 74% yield (entry 6). The lack of any amidic hydrogen atoms in tertiary ketoamide **10b** resulted in a decreased thermal sensitivity of the substrate, and the cycloaddition process could proceed satisfactorily under thermal activation (entry 7). Conversion and yield, however, proved low, due to the lower electron-withdrawing ability of

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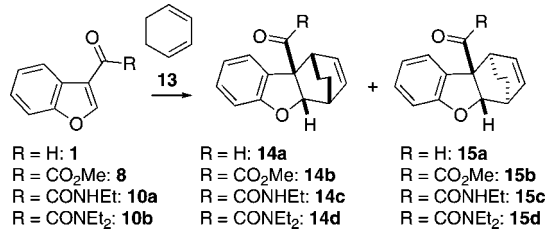
TABLE 2. Reaction with Cyclohexadiene 13

entry	substrate	T (°C)	time (h)	pressure (GPa)	Lewis acid	solvent	adducts	conv[a] (%)	yield (%)	endo/exo (**14**/**15**) ratio[b]
1	**1**	200[c]	70			toluene	**14a/15a**	70	60	40:60
2	**8**	190[c]	96			toluene	**14b/15b**	98	94	13:87
3	**10a**	190[c]	72			toluene	**14c/15c**	70	64	15:85
4	**10a**	110	60		$ZnCl_2$[d]	toluene	**14c/15c**	80	78	3:97
5	**10a**	25	96	1.2		THF		3	*e*	*e*
6	**10a**	50	60	1.6	$ZnCl_2$[d]	THF	**15c**	100	79	0:100
7	**10b**	210[c]	48			toluene	**14d/15d**	45	35	50:50
8	**10b**	110	60		$ZnCl_2$[d]	toluene	*c*	<5	*c*	*c*
7	**10b**	50	60	1.6	$ZnCl_2$[d]	THF	**14d/15d**	100	52[f]	25/75

[a] Conversion. [b] Determined by NMR spectrometry on the crude reaction mixtures. [c] Conducted in a sealed tube. [d] 10 mol %. [e] Not determined. [f] The formation of polymeric materials renders isolation of the products difficult.

SCHEME 3



SCHEME 4

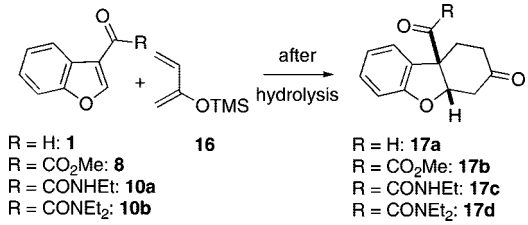


TABLE 3. Reaction with 2-Trimethylsilyloxybutadiene (16)

entry	substrate	T (°C)	time (h)	pressure (GPa)	solvent	adducts	conv[a] (%)	yield (%)
1	**1**	170[b]	70		toluene		100	0[c]
2	**1**	50	60	1.5	THF	**17a**	90	20[d]
3	**8**	170[b]	72		toluene	**17b**	100	83
4	**8**	50	48	1.5	THF	**17b**	100	78
5	**10a**	170[b]	72		toluene		0	
6	**10a**	20	24	1.6	THF	**17c**	95	74
7	**10b**	175[b]	84		toluene	**17d**	45	31
8	**10b**	50	48	1.6	THF	**17d**	100	73

[a] Conversion. [b] Conducted in a sealed tube. [c] Degradation of the reaction mixture. [d] Sensitivity of the cycloadduct to purification conditions.

the substituent. Here again, the problem was solved by carrying out the reaction under 1.6 GPa. These conditions completely converted the aromatic bicycle into the expected tricyclic compound **17d**, which was isolated in 73% yield.

To gain a more complete understanding of the behavior of benzofurans in the normal electron demand [4 + 2] cycloaddition reaction and widen the scope of the process, we next considered their interaction with the highly functonalized 1-methoxy-3-trimethylsilyloxybutadiene (**18**) (Danishefsky's diene) (Scheme 5). The thermal sensitivities of benzofuran **1** and 4-π component **18** led to a complete degradation of the substrates when conducting the cycloaddition process at 170 °C (Table 4, entry 1). Here again, the milder high pressure activation proved efficient and induced a nearly complete reaction at 1.2 GPa (entry 2) and a complete one at 1.6 GPa (entry 3). Hydrolysis of the silyl enol ether moiety in the crude sample proved tricky under classical conditions (TFA, Bu_4NF, or SiO_2/MeOH),[21] leading to partial decomposition of the products and irreproducible results. The use of ammonium fluoride proved best and allowed to isolate the generated cycloadducts in higher yields. Two structurally different cycloadducts could be isolated in this case, arising from two competitive pathways involving either the C-2/C-3 benzofuranyl double bond, leading to **19a**, or the formyl C═O bond, generating **20a**, after hydrolysis. Chemoselectivity expectedly proved to highly favor the Diels−Ader (DA) over the hetero-Diels−Alder (HDA) process, and the pressure parameter displayed a strong influence on this issue. The optimal conversion/DA ratio was attained when effecting the reaction at 1.2 GPa pressure, which led to a 92% conversion rate and a 94% selectivity in favor of the Diels−Alder adduct (entry 2). Conversion rate benefited from a higher 1.6 GPa, but at the expense of chemoselectivity (entry 3). Here again, benzofuran **8** proved more robust, and the thermally activated cycloaddition process led to a complete conversion of the starting material (entry 4). Two adducts **19b** and **21b** arising from competitive DA and HDA reactions were again obtained in a now reversed 30/70 ratio, and isolated in 26 and 60% yields, respectively. In this case, hydrolysis of the heterocycloadduct led to a concomitant loss of methanol and oxacyclohexenone **21b** was isolated. Noteworthy is the complete *exo* selectivity of the DA process. Lewis acid activation induced a totally HDA-selective reaction and led to heterocycloadduct **21b**, isolated in 62% yield (entry 5). In contrast, high pressure activation appeared to disfavor the HDA process in this case: compressing benzofuran **8** with a 5-fold excess of diene **18** at 1.2 GPa led to a total consumption of the starting material. ^{1}H NMR spectrometry analysis indicated the presence of a structurally different adduct. Hydrolysis of the crude mixture and chromatography led to isolation of compound **22b**, resulting from the interaction of benzofuran **8** with 2 equiv of diene **18**, in 77% yield (entry 6). This compound thus arises from a double, sequential cycloaddition process on (i) the C_2═C_3 benzofuranyl double bond and (ii) the C═O group of the ketoester moiety. The amount of diene was decreased in an attempt to maximize the formation of monoadduct **19b**. Thus, the use of only 1 equiv of diene led to a 80% conversion of **8** and furnished a 92:8 mixture of **19b/22b**, isolated in 59 and 4% yields, respectively (entry 7). Ketoamide substituted benzofuran **10a** expectedly appeared less prone to heterocycloaddition reactions. The thermal cycloaddition reaction between **10a** and Danishefsky's diene **18** led, after ammonium fluoride treatment, to the exclusive formation of DA-monoadduct **19c**, isolated in 75% yield as a unique *exo* diastereomer (entry 8).

SCHEME 5

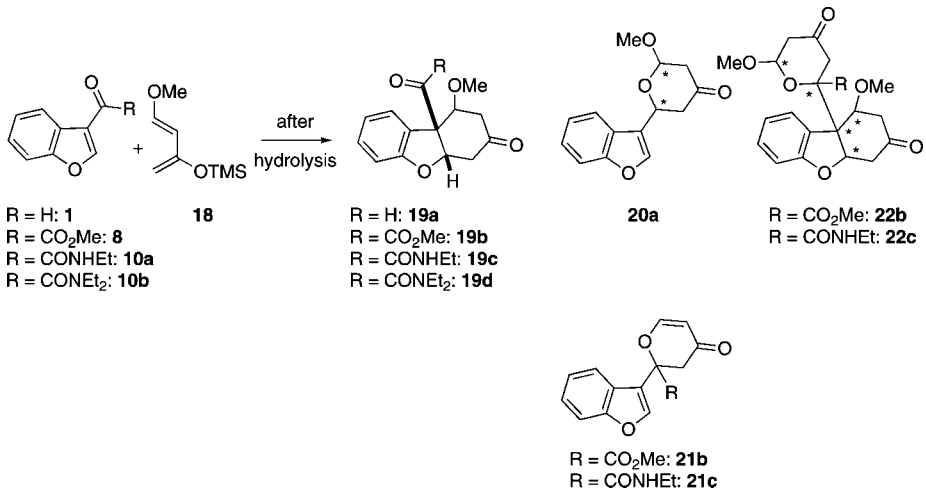


TABLE 4. Reaction with Danishefsky's Diene 18

entry	substrate	*T* (°C)	**18** (equiv)	time (h)	pressure (GPa)	Lewis acid	solvent	adducts	DA-/HDA-/bis-adduct ratio[a]	conv[b] (%)	yield (%) (adduct yield)[c]	endo/exo ratio for **19**[d]
1	**1**	170[e]	5	70			Toluene			100	0	
2	**1**	20	5	48	1.2		THF	**19a/20a**	94/6/0	92	52 (52/0)	18/82
3	**1**	20	5	60	1.6		THF	**19a/20a**	75/25/0	100	38 (29/9)	0/100
4	**8**	165[e]	5	48			Toluene	**19b/21b**	30/70/0	100	86 (26/60)	0/100
5	**8**	20	5	192		$ZnCl_2$[f]	CH_2Cl_2	**21b**	0/100/0	100	62	
6	**8**	20	5	24	1.2		THF	**22b**	0/0/100	100	77	
7	**8**	20	1	8	1.2		THF	**19b**	92/0/8	80	63 (59/4)	0/100
8	**10a**	165[e]	5	72			Toluene	**19c**	100/0/0	100	75	0/100
9	**10a**	20	5	60		$ZnCl_2$[f]	CH_2Cl_2	**21c**	0/100/0	85	54	
10	**10a**	20	5	24	1.2		THF	**19c/22c**	45/0/55	100	77 (37/40)	
11	**10a**	20	2	60	1.2		THF	**19c/22c**	82/0/18	100	81 (73/8)	8/92
12	**10a**	20	1	108	1.2		THF	**19c**	100/0/0	85	60	5/95
13	**10b**	175[e]	5	60			Toluene	**19d**	100/0/0	100	87	15/85
13	**10b**	20	5	24	1.2		THF	**19d**	100/0/0	100	87	75/25

[a] Diels−Alder adduct (**19**)/hetero-Diels−Alder adduct (**20**) or (**21**)/bis-adduct (**22**) ratio. [b] Conversion. [c] DA-/HDA-/bis-adduct yield. [d] Determined by NMR spectrometry on the crude reaction mixtures. [e] Conducted in a sealed tube. [f] 10 mol %.

In contrast, Lewis acid activation led to a completely different reaction outcome, and the exclusive formation of the HDA-cycloadduct **21c** was observed (entry 9). We and others previously reported the two documented examples of involvement of secondary ketoamide moieties in hetero-Diels−Alder reactions.[21b,23] High-pressure activation allowed the double DA/HDA cycloaddition process to also take place. When a 5-fold excess of diene was used, a 45:55 mixture of monoadduct **19c** and bis-adduct **22c** was observed (entry 10). Decreasing the quantity of diene allowed us to increase the amount of monoadduct **19c** at the expense of bisadduct **22c** (entries 11 and 12), whose formation was completely suppressed when using only 1 equiv of diene. In the absence of any amidic hydrogen atom, in the case of tertiary ketoamide **10b**, no heterocycloaddition was observed, regardless of any excess amount of substrate. Both the thermal and high pressure activation of the cycloaddition led to a unique DA cycloadduct **19d**, isolated in very good yields after ammonium fluoride hydrolysis (entries 13 and 14). The activation mode has an important impact on the diastereoselectivity of the reaction since the *endo*/*exo* ratios were reversed depending on the reaction conditions: while heating favors the formation of the *exo* adduct,

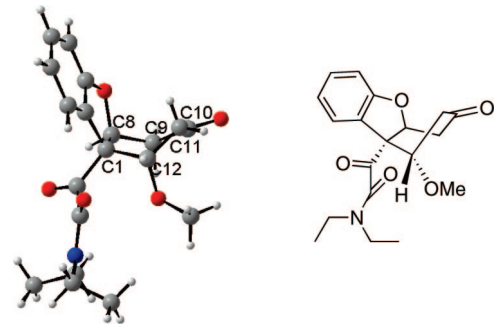


FIGURE 2. Ball and stick drawing of *exo*-**19d**.

presumably for steric reasons, the *endo* diastereomer is preferably formed under high pressure, probably due to compactness of the corresponding transition state in this case.[24] The stereochemistry of the cycloadducts has been unambiguously assigned by single-crystal X-ray diffraction analysis. The solid-state conformation of the *exo* diastereomer of **19d**, depicted in Figure 2, features a relative *cis* relationship between the methoxy and the angular ketoamide groups.

In order to get further insight into the mechanistic details of the cycloaddition, we examined the course of these reactions

(23) (a) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497–502. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087–2095.

(24) For similar observations, see: (a) Pichon, N.; Harrison-Marchand, A.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2004**, *69*, 7220.

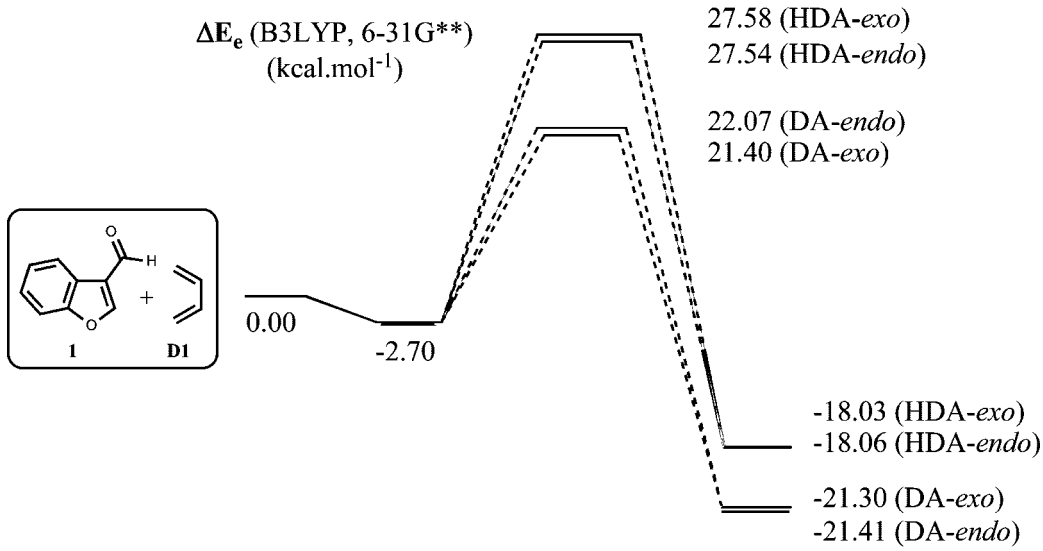


FIGURE 3. Schematic representation of the energy profiles for the cycloaddition between **1** and **D1**.

TABLE 5

entry	dienophile	diene	calc method	ΔE_e VdW complex[a] (kcal/mol)	ΔE_e TS DA endo[b] (kcal/mol)	ΔE_e TS DA exo[b] (kcal/mol)	ΔE_e TS HDA endo[b] (kcal/mol)	ΔE_e TS HDA exo[b] (kcal/mol)	ΔE_e CA DA endo[c] (kcal/mol)	ΔE_e CA DA exo[c] (kcal/mol)	ΔE_e CA HDA endo[c] (kcal/mol)	ΔE_e CA HDA exo[c] (kcal/mol)
1	**1**	**D1**	B3LYP 6-31G**	−2.70	22.07	21.40	27.54	27.58	−21.41	−21.30	−18.06	−18.03
2	**1**	**D1**	B3PW91 6-31G**	−1.82	19.78	18.93	25.18	25.25	−27.80	−25.14	−23.60	−23.57
3	**1**	**D1**	B3LYP 6-31+G**	−1.27	23.73	23.53	30.04	30.17	−18.40	−18.36	−14.69	−14.68
4	**1**	**D1**	B3LYP 6-31G**[d]	−1.44	21.39	20.98	28.53	28.68	−20.48	−20.11	16.05	−16.08
5	**1-BF_3**	**D1**	B3LYP 6-31G**	−4.84	13.83	12.07	16.19	18.73	−18.35	−15.81	−15.39	−11.45
6	**1**	**D2**	B3LYP 6-31G**	−3.09	18.76	17.65	21.88	21.94	−3.03	−3.04	−9.26	−12.35

[a] Energy difference between the Van der Waals complex and the sum of substrates. [b] Energy difference between the optimized transition state and the sum of substrates. [c] Energy difference between the optimized cycloadduct and the sum of substrates. [d] Single-point calculations effected by applying the conductor polarizable continuum model (THF).

by computational means. We first studied the model reaction of 3-formylbenzofuran (**1**) with 1,3-butadiene (**D1**). Evaluation of the frontier orbitals energies confirmed the preferential interaction between the HOMO of diene **D1** and the LUMO of dienophile **1** and thus the normal electron demand character of the cycloaddition process. Depending on the structure of the diene, experimental results revealed a possible competition between DA and HDA cycloaddition processes. Thus, quantitative evaluation of the prefered pathway (DA/HDA) on the activation energy was then undertaken, considering that the reaction is under kinetic control, by localization of the transition state (TS) of the cycloaddition between butadiene **D1** and 3-formylbenzofuran (**1**).[25] *s-cis* and *s-trans* conformations of the $C_2{=}C_3{-}C{=}O$ moiety of dienophilic benzofuran **1** were considered, and the most stable s-*trans* conformer (stabilized by 1.69 kcal·mol^{-1}) was used and kept all along the reaction path calculations. For diene component **D1**, only the reactive *s-cis* conformation was considered, an energy minimum being found for the conformer featuring a $C{=}C{-}C{=}C$ dihedral angle of 30.4°. The two routes (DA/HDA), combined with the e*ndo*/*exo* approaches of the diene allow for four different transition states. Various Van der Waals (VdW) complexes between the dienophile and diene were found, and the most stable was 2.70 kcal·mol^{-1} below the reactants (Figure 3 and Table 5, entry 1). The exothermicities of the DA and HDA cycloadditions were found to amount to 21.41 and 18.06 kcal·mol^{-1}, respectively, confirming the kinetic control postulated above. The most favored transition states were found to be 21.40 kcal·mol^{-1} above the reactants for the DA process (*exo* approach) and 27.54 for the HDA (*endo* approach). For both routes, the difference between the activation energies of the *endo* and *exo* attacks were small, within 0.7 kcal·mol^{-1}. These data are in line with the experimental results, since no HDA-cycloadducts were formed when reacting the structurally related 2,3-dimethylbutadiene (**11**) with benzofuranyl derivatives. The asynchronicity of the DA process is highlighted by the large difference between the lengths of the forming bonds at the TS, the shorter being expectedly the one between carbon α to the heteroatom and one end of the symmetrical diene. For instance, the most favored DA-*exo* TS is characterized by a $C_2{-}C_{diene}$ of 1.90 Å and a $C_3{-}C_{diene}$ of 2.78 Å. Astonishingly however, the HDA process appears less asynchronous ($C{-}C_{diene}$ and $O{-}C_{diene}$ of 2.07 and 2.01 Å, respectively). A small displacement of the nuclear coordinates at the TSs toward the reaction products directly led to cycloadducts and confirmed the concerted nature of both DA and HDA processes. All attempts to find zwitterionic intermediates were unsuccessful.

The validity of the method was checked by performing similar calculations using a different functional (B3PW91) or a larger basis set such as 6-31+G**. The same trends were found in both cases (Table 5, entries 2 and 3). The effects of solvent (THF), generally considered as of little influence in DA reactions, was also evaluated by applying the conductor polariz-

(25) The nature of the TS was checked via harmonic frequency evaluations to show the presence of one and only one imaginary frequency. In addition, the TS structures were given small geometrical perturbations along the reaction coordinates and then further geometrical optimization was carried out to ensure they connect the reactant and product of interest.

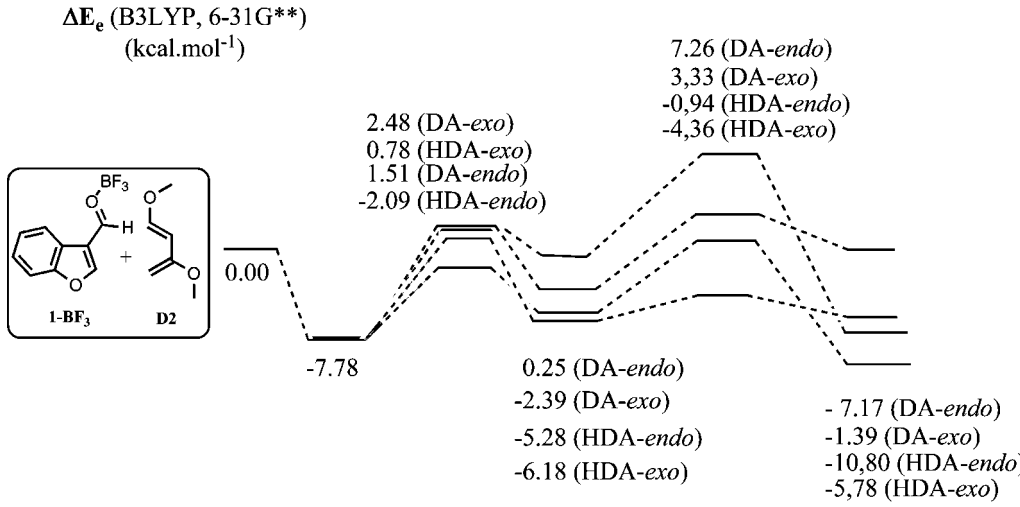


FIGURE 4. Schematic representation of the energy profiles for the BF_3-catalyzed cycloaddition between **1** and **D2**.

able continuum model to the previous results (entry 3). The same trends were observed but the energy differences between both pathways (DA/HDA) were slighlty enhanced. Thus, all further calculations were effected at the B3LYP/6-31G** level in the absence of any continuum effect.

Experimental results revealed a strong influence of the Lewis acid catalysis on the chemoselectivity of the cycloaddition process (compare for instance entries 4, 5, 6, and 7 or entries 8, 9, 10, and 11 of Table 4). We thus investigated this phenomenon by introducing trifluoroborate (BF_3) as a model Lewis acid compatible with the calculation method. Competitive complexation of the two oxygen atoms of benzofuran **1** was considered. Expectedly, the oxygen atom of the carbonyl group revealed to be the strongest Lewis base, the corresponding complex being 8.99 kcal·mol^{-1} more stable than the one coordinated to the benzofuranyl oxygen atom. The *s-trans* conformer proved more stable than its *s-cis* counterpart and the complexation energy was evaluated at −13.91 kcal·mol^{-1}, the optimized complex featuring an O−B length of 1.70 Å. The complexation energy appeared slighly higher for the benzofuranyl substrate than for the cycloadducts (in the 7.34−11.24 kcal·mol^{-1} range). Starting from this BF_3-coordinated conformer, the energy profile of the cycloadditions appeared alike the uncatalyzed one. Here again, a VdW complex between the diene and the BF_3 coordinated dienophile was located 4.84 kcal·mol^{-1} below the reactants (Table 5, entry 5). The most favored transition states were found to be 12.07 kcal·mol^{-1} above the reactants for the DA process (*exo* approach) and 16.19 for the HDA (*endo* approach). Alike the uncatalyzed systems described above, the activation energies were significantly decreased (by more than 8 kcal·mol^{-1} in each case), confirming the positive effect of the Lewis acid on the course of the cycloaddition process. The energy difference between both DA and HDA pathways also appeared smaller than in the uncatalyzed case but still remained in favor of the DA process, with this symmetrical unsubstituted diene. The HDA process appeared much more asynchronous in this case. For instance, the most favored *endo* TS is characterized by a C−C_{diene} of 1.76 Å and a O−C_{diene} of 2.45 Å. A small displacement of the nuclear coordinates at the TSs toward the reaction products directly led to cycloadducts, confirming, here again, the concertdness of the cycloadditions in the presence of a Lewis acid.

We next examined the influence of the diene structure on the course of these reactions and chose to study the cycloadditions with unsymmetrical polarized dienes. 1,3-Dimethoxybuta-1,3-diene was chosen as a model for the computationally demanding 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (**18**). When considering the *s-cis* diene conformation, four possible reactive structures can be defined depending on the *s-cis* or *s-trans* conformational nature of both C=C−O−CH_3 moieties,[26] and the most stable s-*cis*-s-*cis* conformer was used in the calculations. Evaluation of the frontier orbitals energies confirmed the preferential interaction between the HOMO of diene **D2** and the LUMO of dienophile **1** and, thus, the normal electron demand of the cycloaddition process. Compared to butadiene **D1**, the presence of two electron-donating substituents on **D2** enhances the HOMO energy and facilitates the cycloaddition process by decreasing the energy difference between the frontier orbital energies. These results were confirmed by localization of the transition states, since the activation energies appeared smaller than in the case of butadiene **D1** (Table 5, compare entries 1 and 6). Here again, the DA process appeared favored over the HDA one, by 4.23 kcal·mol^{-1}, and the difference between the activation energies of the *endo* and *exo* attacks remained negligible, within 1.1 kcal·mol^{-1}. To be noted is the fact that these reactions were found to be much less exothermic with this diene, especially for the DA adducts, which were found to lie about 3 kcal·mol^{-1} below the starting materials. In this case and in contrast to what was observed in the case of unsubstituted diene, HDA adducts were found to be the thermodynamic products. These results are in line with the experimental results for the cycloaddition between **1** and **18** (Table 4, entries 2 and 3), which showed a significant preference for the formation of the DA adducts but also a slight formation of HDA adducts in some cases, which were not observed with the less activated diene **D1** (Tables 1−3). Obviously, these data do not reflect the observed pressure effect, which are not taken into account in the calculations.[27]

We next studied the same sequence with 1,3-dimethoxybutadiene **D2** in the presence of BF_3 as Lewis acid. In contrast to all previous results, the energy profile appeared different in this case (Figure 4): a stepwise mechanism, involving formation of the C_2−$C_{4(diene)}$ and $C_{carbonyl}$−$C_{4(diene)}$ in the first step, for the DA and HDA processes, respectively, was the only one located

(26) Baki, S.; Maddaluno, J.; Derdour, A.; Chaquin, P. *Eur. J. Org. Chem.* **2008**, 3200–3208.
(27) Dumas, F.; Fressigne, C.; Langlet, J.; Giessner-Prettre, C. *J. Org. Chem.* **1999**, *64*, 4725.

from a computational point of view. The rate-determining step appeared highly dependent on both the chemoselectivity (DA vs HDA) and the stereoarrangement (*endo vs exo*): it appears that, in contrast to the concerted mechanism, stereoelectronic effects play a major role on the course of the reaction. The HDA primary process was found to be favored over the DA one by a significant 3.60 kcal·mol^{-1}. The activation energies were smaller than in the uncomplexed system, confirming, here again, the positive influence of the Lewis acid on the course of the cycloaddition. In this case, HDA adducts were found to be both the kinetic and thermodynamic products. This finding is in total agreement with the experimental results; the Lewis acid catalyzed cycloadditions between **8** or **10a** and **18** exclusively led to the HDA adduct (Table 4, entries 5 and 9). We thus evidenced that the cycloadditions between benzofurans and electron-rich dienes are possible either through concerted or stepwise mechanisms. The concerted one appears more favorable with unpolarized dienes while the stepwise alternative is preferred with a polarized diene under acid catalysis. Obviously, the experimental limit between these two possible mechanisms is not clear-cut. Thus, a fine-tuning of parameters such as the solvent (protic or not), the pressure or the nature of the Lewis acid catalyst can have a dramatic influence on the prefered cycloaddition pathway and could be experimentally taken to advantage.

Conclusion

The results described in this paper show that a variety of electron-poor benzofurans can behave as dienophiles in normal electron demand [4 + 2] cycloadditions. The dearomatized products arising from the reaction depends on (i) the type of the electron-withdrawing substituent on position 3 of the benzofuran, (ii) the diene involved in the cycloaddition process, and (iii) the method of activation. Thus, the reaction between electron-poor benzofuranyl aromatics and all-carbon dienes such as 2,3-dimethylbuta-1,3-diene or cyclohexadiene yields the expected Diels−Alder adducts **12** or **14/15**. With the less reactive cyclohexadiene, biactivation with zinc chloride and pressures up to 1.6 GPa appears well-suited, leading to the expected cycloadducts in better yields and higher *exo*selectivities under milder thermal conditions. The use of sensitive dienes such as 2-trimethylsilyloxybutadiene also shows the limits of the classical thermal activation and higher yields are obtained under hyperbaric conditions. The involvment of the strongly enriched Danishefsky's diene induces a competition for the reactivity site. The prefered dienophilic partner is unambiguously the aromatic 2,3-carbon−carbon double bond, furnishing the tricyclic adducts **19**. However, the carbonylated unit in position 3 can become a competitive dienophile with substrates prone to heterocycloaddition such as **1**, **8**, or **10a**, in particular under Lewis acid activation. The sequential involvement of the aromatic double bond and the carbonyl moiety as dienophiles is also possible by using a large excess of diene under high pressure activation, leading to the formation of bis-adducts **22**.

In line with the experimental results, the DFT computational studies indicate that, in most cases, the Diels−Alder pathway, involving the reaction between the C_2-C_3 aromatic double bond, is preferred over the hetero-Diels−Alder route through an asynchronous concerted transition state. However, the cycloaddition between the model BF_3-coordinated benzofuran and 1,3-dimethoxybutadiene appears to favor the heterocycloaddition pathway through a stepwise mechanism involving the formation of the C−O bond in the second step of the process.

The cycloadducts thereby produced and the stereochemistry charaterizing the newly created stereocenters show possible applications of this methodology in the realm of alkaloids synthesis. Further work is in progress in these laboratories and will be reported in due time.

Experimental Section

Representative Procedure for the Amidification of Benzofuran-3-yloxoacetic Acid (9) with Ethylamine. To a solution of benzofuran-3-yloxoacetic acid (**9**) (0.53 g, 2.79 mmol) in 22 mL of CH_2Cl_2 were successively added pyridine (0.68 mL, 8.36 mmol) and $(COCl)_2$ (0.54 mL, 6.13 mmol), in one portion, at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then 1 h at room temperature. After evaporation of the volatiles under reduced pressure, the crude ketoacyl chloride was dissolved in CH_2Cl_2, and *i*-Pr_2EtN (0.93 mL, 5.57 mmol) was added at 0 °C. After 15 min, a 1 M THF solution of ethylamine (2.80 mL, 5.57 mmol) was added dropwise. The resulting mixture was stirred for 45 min at 0 °C and then 1 h at room temperature. Water was added, and the mixture was extracted with EtOAc (3 times). The combined organic layers were dried over $MgSO_4$, and the solvents were concentrated under reduced pressure. The crude product was purified by flash chromatography on silica (EtOAc/cyclohexane 25:75) to afford **10a** was obtained as a bright yellow solid (0.495 g, 82%, mp 69 °C): ^{1}H NMR δ 1.26 (t, J = 6.0 Hz, 3H), 3.40−3.49 (m, 2H), 7.33 (bs, 1H), 7.37−7.42 (m, 2H), 7.54−7.60 (m, 1H), 8.23−8.28 (m, 1H), 9.37 (s, 1H); ^{13}C NMR δ 14.6, 34.5, 111.7, 117.6, 122.7, 124.7, 125.0, 126.0, 154.8, 157.7, 160.6, 182.6; IR (NaCl) ν 3384, 3142, 2976, 2969, 2801, 1691, 1640, 1519, 1448, 1257 cm^{-1}; MS (EI) *m/z* (relative intensity) 217 [M$^{+\bullet}$] (23), 145 (100), 89 (48), 72 (22), 63 (28), 44 (40). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.49; H, 5.16; N, 6.33.

Representative Procedure for the Cycloaddition of Benzofuran 8 with 2,3-Dimethylbutadiene (11). Thermal Activation. A pressure tube containing benzofuran **8** (0.204 g, 1 mmol) and 2,3-dimethylbutadiene (**11**) (0.56 mL, 5 mmol) in anhydrous degassed toluene (4 mL) was sealed under argon and heated in a sand bath at 180 °C for 48 h. After cooling, the solvents and excess of diene were removed under reduced pressure and the residue was was purified by flash chromatography on silica (EtOAc/cyclohexane 2:8) to yield **12b** as a bright yellow solid (0.271 g, 95%, mp 66 °C): ^{1}H NMR δ 1.57 (s, 3H), 1.69 (s, 3H), 2.41−2.76 (m, 4H), 3.74 (s, 3H), 5.46 (dd, J = 4.9, 4.9 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 6.82 (ddd, J = 1.1, 7.0, 7.0 Hz, 1H), 7.10−7.17 (m, 2H); ^{13}C NMR δ 19.4, 19.5, 36.1, 37.1, 52.8, 62.2, 84.6, 109.5, 120.5, 124.4, 125.4, 126.3, 127.0, 130.0, 161.1, 162.5, 194.0; IR (NaCl) ν 3044, 2938, 2924, 2853, 1738, 1596, 1479 cm^{-1}; MS (EI) *m/z* (relative intensity) 286 [M$^{+\bullet}$] (18), 199 (100), 171 (13), 145 (17). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.41.

Representative Procedure for the Cycloaddition of Benzofuran 10a with 1,3-Cyclohexadiene (13). High Pressure and Lewis Acid Activation. To a stirring solution of benzofuran **10a** (0.043 g, 0.20 mmol) in anhydrous THF (0.9 mL) was added $ZnCl_2$ (0.003 g, 0.02 mmol) at room temperature. The mixture was stirred for 30 min. Distilled 1,3-cyclohexadiene (**13**) (0.10 mL, 1 mmol) was then added, and the resulting mixture was transferred into a high-pressure vessel and compressed at 1.6 GPa, 50 °C for 60 h. After decompression, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica (EtOAc/cyclohexane 1:9 − 2:8) to give **15c** as a yellow oil (0.047 g, 79%): ^{1}H NMR (CD_3CN) δ 1.02 (t, J = 7.3 Hz, 3H), 1.06−1.17 (m, 3H), 1.67−1.75 (m, 1H), 3.00−3.02 (m, 1H), 3.09−3.19 (dq, J = 1.1, 7.3 Hz, 2H), 3.45−3.47 (m, 1H), 5.27 (dd, J = 0.9, 4.1 Hz, 1H), 6.17 (ddd, J = 0.9, 7.9, 7.9 Hz, 1H), 6.40−6.45 (m, 1H), 6.78−6.85 (m, 2H), 7.14−7.23 (m, 2H), 7.31 (bs,1H); ^{13}C NMR δ

14.5, 17.0, 21.1, 27.0, 34.2, 35.3, 65.0, 86.3, 110.0, 120.3, 125.4, 125.8, 130.3, 131.5, 136.0, 158.9, 161.9, 195.0; IR (NaCl) ν 3391, 3047, 3014, 2932, 2857, 1681, 1476, 1241, 1157 cm^{-1}; MS (CI, *i*-butane) *m/z* (relative intensity) 298 $[M + H]^+$ (100); HRMS calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$ 298.1444, found 298.1457.

Representative Procedure for the Cycloaddition of Benzofuran 10b with 2-Trimethylsilyloxybutadiene (16). High-Pressure Activation. To a solution of benzofuran **10b** (0.049 g, 0.2 mmol) in anhydrous THF (0.9 mL), stirred at room temperature under argon, was added 2-trimethylsilyloxybutadiene (**16**) (0.142 g, 1 mmol). The resulting mixture was transferred into a high-pressure vessel and compressed at 1.6 GPa, 50 °C for 48 h. After decompression, the solvent and excess of diene were removed under reduced pressure. The excess diene was removed by bulb-to-bulb distillation under reduced pressure (60 °C/0.2 mmHg). The residue was dissolved in MeOH (5 mL), SiO_2 was added, and the mixture was stirred overnight. The reaction mixture was filtered over Celite, washed with EtOAc, and purified by flash chromatography on silica (EtOAc/cyclohexane 1:9 to 3:7) to furnish **17d** as a colorless oil (0.046 g, 73%): ^1H NMR δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 3H), 1.91−2.04 (m, 1H), 2.30−2.38 (m, 1H), 2.55−2.60 (m, 2H), 2.87−2.94 (m, 4H), 3.25−3.47 (m, 2H), 5.52 (dd, $J = 3.8$, 3.8 Hz, 1H), 6.78 (d, $J = 7.5$ Hz, 1H), 6.93 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.21 (ddd, $J = 1.2$, 7.5, 7.5 Hz, 1H), 7.34 (dd, $J = 1.2$, 7.5 Hz, 1H); ^{13}C NMR δ 12.5, 13.8, 31.6, 35.3, 38.9, 42.1, 42.5, 59.3, 82.6, 110.3, 121.8, 124.7, 125.3, 130.6, 159.7, 166.0, 200.7, 208.1; IR (NaCl) ν 2976, 2935, 2842, 1723, 1640, 1478, 1462, 1252 cm^{-1}; MS (EI) *m/z* (relative intensity) 315 $[M^{+\bullet}]$ (3), 187 (49), 131 (33), 100 (100), 72 (71), 55 (97). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.49; H, 6.86; N, 4.45.

Representative Procedure for the Cycloaddition of Benzofuran 8 with 1-Methoxy-3-trimethylsilyloxybutadiene (18). High-Pressure Activation. To a solution of benzofuran **8** (0.204 g, 1 mmol) in anhydrous THF (5.5 mL) at room temperature under argon, was added Danishefsky's diene **18** (0.195 mL, 1 mmol). The resulting mixture was transferred into a high-pressure vessel and compressed at 1.2 GPa for 8 h. After decompression, the solvent was removed under reduced pressure. The excess of diene was removed by bulb-to-bulb distillation under reduced pressure (60 °C/0.2 mmHg). The residue was dissolved in MeOH (5 mL), and NH_4F (0.040 g, 1 mmol) was added at −30 °C. The resulting mixture was stirred for 15 min and was then concentrated under reduced pressure. Purification by flash chromatography on Florisil (EtOAc/cyclohexane 1:9−1:1) afforded **19b** (0.170 g, 56%): ^1H NMR δ 2.04 (dd, $J = 1.9$, 18.1 Hz, 1H), 2.65 (dd, $J = 3.8$, 18.1 Hz, 1H), 2.73 (dd, $J = 3.4$, 18.1 Hz, 1H), 2.89 (dd, $J = 3.0$, 18.1, 1H), 3.14 (s, 3H), 3.89 (s, 3H), 4.55−4.56 (m, 1H), 5.78 (dd, $J = 3.4$, 3.8 Hz, 1H), 6.74 (dd, $J = 0.8$, 7.9 Hz, 1H), 6.87 (ddd, $J = 0.8$, 7.9, 7.9 Hz, 1H), 7.17 (ddd, $J = 1.1$, 7.9, 7.9 Hz, 1H), 7.69 (dd, $J = 1.1$, 7.9 Hz, 1H); ^{13}C NMR δ 37.6, 40.9, 53.2, 56.2, 63.2, 80.6, 81.2, 110.6, 121.7, 125.3, 126.4, 131.0, 159.4, 161.6, 190.0, 205.9; IR (NaCl) ν 3072, 3066, 3028, 2953, 2931, 2832, 1732, 1591, 1477, 1281 cm^{-1}; MS (EI) *m/z* (relative intensity) 304 $[M^{+\bullet}]$ (25), 145 (100), 131 (67), 100 (46); HRMS calcd for $C_{16}H_{17}O_6$ $[M + H]^+$ 305.1059, found 305.1025.

Lewis Acid Activation. To a stirring solution of the benzofuran **8** (0.100 g, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added $ZnCl_2$ (0.007 g, 0.05 mmol) at room temperature. The mixture was stirred for 30 min, and Danishefsky's diene **18** (0.480 mL, 2.5 mmol) was then added. After 192 h stirring at room temperature, the solvent was removed under reduced pressure. Excess diene was then removed by bulb-to-bulb distillation under reduced pressure (60 °C/0.2 mmHg). The residue was dissolved in MeOH (5 mL), SiO_2 was added, and the mixture was stirred overnight. The reaction mixture was filtered over Celite, washed with EtOAc, and then purified by flash chromatography on silica (EtOAc/cyclohexane 1:9−3:7) afforded**21b** as a white solid (0.084 g, 62%, mp 114 °C): ^1H NMR δ 3.11 (d, $J = 16.6$ Hz, 1H), 3.34 (d, $J = 16.6$ Hz, 1H), 3.65 (s, 3H), 5.40 (d, $J = 6.0$ Hz, 1H), 7.14−7.26 (m, 2H), 7.31 (d, $J = 6.0$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.58 (s, 1H), 7.67 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR δ 43.2, 53.8, 82.4, 108.2, 112.0, 117.8, 121.4, 123.6, 124.4, 125.4, 143.5, 155.8, 160.9, 169.2, 189.3; IR (NaCl) ν 3152, 3107, 3075, 2955, 2933, 2848, 1746, 1682, 1599, 1453, 1273 cm^{-1}; MS (CI, *i*-butane) *m/z* (relative intensity) 273 $[M + H]^+$ (100). Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.19; H, 4.42.

High-Pressure Activation in the Presence of an Excess of Diene. To a solution of benzofuran **8** (0.100 g, 0.49 mmol) in anhydrous CH_2Cl_2 (1.8 mL), at room temperature, under argon, was added Danishefsky's diene **18** (0.48 mL, 2.45 mmol). The resulting mixture was transferred into a high-pressure vessel and compressed at 1.2 GPa for 24 h. After decompression, the solvent was removed under reduced pressure. The excess diene was removed by bulb-to-bulb distillation under reduced pressure (60 °C/0.2 mmHg). The residue was dissolved in MeOH (5 mL), SiO_2 was added, and the mixture was stirred overnight. The reaction mixture was filtered over Celite, washed with EtOAc, and purified by flash chromatography on silica (EtOAc/cyclohexane 1:9−1:1) furnished **22b** as a white solid (0.145 g, 73%): ^1H NMR δ 1.92 (dd, $J = 2.3$, 18.5 Hz, 1H), 2.45 (d, $J = 3.8$ Hz, 2H), 2.59 (dd, $J = 3.4$, 18.5 Hz, 1H), 2.71−3.13 (m, 4H), 3.24 (s, 3H), 3.59 (s, 3H), 3.62 (s, 3H), 4.20 (m, 1H), 5.20 (dd, $J = 4.1$, 4.1 Hz, 1H), 5.85 (m, 1H), 6.74 (d, $J = 8.1$ Hz, 1H), 6.83 (ddd, $J = 0.8$, 7.6, 7.6 Hz, 1H), 7.17−7.24 (m, 2H); ^{13}C NMR δ 39.2, 43.2, 43.7, 44.0, 52.4, 56.7, 57.2, 78.9, 80.5, 81.6 (2C), 100.3, 110.6, 120.8, 125.9, 126.3, 131.2, 160.4, 173.1, 201.8, 207.5; IR (NaCl) ν 3029, 2948, 2930, 2837, 2930, 1723, 1478, 1461, 1248 cm^{-1}; MS (EI) *m/z* (relative intensity) 404 $[M^{+\bullet}]$ (5), 372 (13), 217 (65), 202 (15), 185 (32), 157 (16), 131 (100), 115 (14), 101 (12), 84 (47). Anal. Calcd for $C_{21}H_{24}O_8$: C, 64.51; H, 5.41. Found: C, 64.46; H, 5.59.

Computational Details. Full geometry optimizations were systematically conducted with no symmetry restraints using the Gaussian 03 program[28] within the framework of the density functional theory (DFT). Unless otherwise mentioned, the hybrid B3LYP exchange-correlation functional[29] was used, associated to the 6-31G** basis set for all atoms. This level of theory has been previously shown to be reliable for similar organic systems[30] and was confirmed from the validation computations reported in this study. Implicit solvation by THF using the PCM model[31] was also examined by single point calculation on the optimized structures and was shown to be of no significant effect: it is thus not used unless otherwise mentionned. Frequencies were evaluated within the harmonic approximation, and the stationary points were characterized in order to verify that minima (reactants, intermediates and adducts) and transition states (TS) have zero and one imaginary frequency, respectively. Thermal and pressure corrections to the

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electronic energy were not taken into account within these computations as they are believed to be of similar effects for DA and HDA processes, and comparison between these two processes should thus not be affected by these corrections.

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Supporting Information Available: Procedures and analytical data for compounds**8**, **14**, **10a**,**b**, **12a**−**d**, **14a**−**15a**, **14b**−**b**, **14d**−**d**, **15c**, **17a**−**d**, **19a**−**d**, **20a**, **21b**,**c**, and **22b**,**c**. Total energy and Cartesian coordinates for **1**, **D1**, **D2**, **C1**−**C3**, **TS1**−**TS4**, **CA1**−**CA4**, **TS5**−**TS8**, **CA5**−**CA8**, **TS5-2**, **TS6-2**, **TS7-2**, **TS8-2**, **CA5-2**, **CA6-2**, **CA7-2**, and**CA8-2**. ^{1}H and ^{13}C spectra for compounds **1**, **12**, **8**, **14**, **10a**,**b**, **12a**−**d**, **14a**−**15a**, **14b**−**15b**, **14d**−**15d**, **15c**, **17a**−**d**, **19a**−**d**, **20a**, **21b**,**c**, and **22b**,**c**. ORTEP drawing for **19d-exo**. This material is available free of charge via the Internet at http://pubs.acs.org.

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