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Influence of Lewis acids on the facial selectivity in cycloadditions of sugar-derived dihydropyranones

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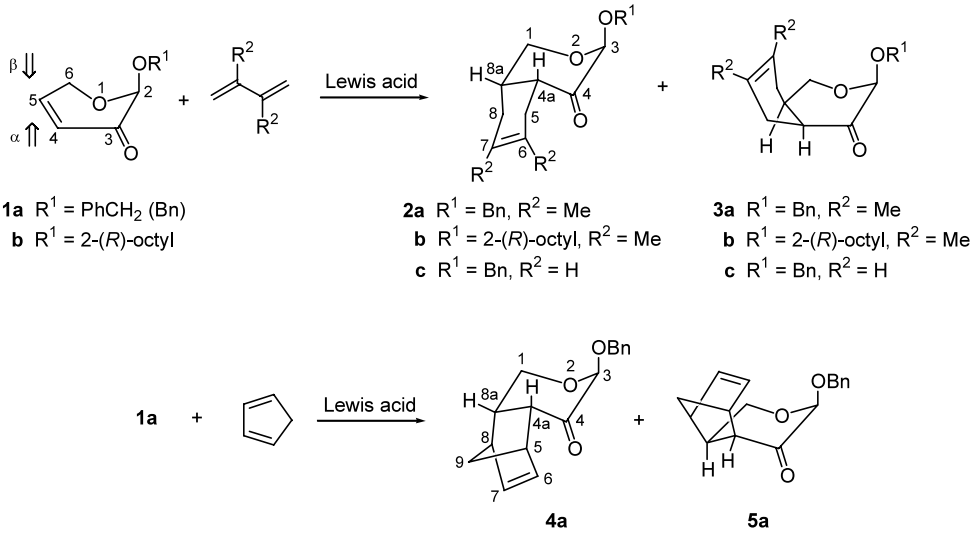
Abstract—The influence of such Lewis acids as $Et_2O{\cdot}BF_3$, $ZnCl_2$, $SnCl_4$ and $TiCl_4$ on the stereochemical course of the Diels–Alder cycloadditions of sugar-derived (2*S*)-alkoxydihydropyranones was studied. The first two catalysts promoted the addition of dienes to give (3*S*,4a*R*,8a*S*)-3-alkoxy-4a,5,8,8a-tetrahydro-2-benzopyran-4-ones, and their concentration had almost no effect on the stereochemistry of the reaction. In contrast, the concentration of $SnCl_4$ and $TiCl_4$ had a remarkable influence on the selectivity, and even facial stereoselection reversal has been observed. These results may be ascribed to chelate complexation of the Lewis acid with the carbonyl and the vicinal alkoxy group of the dihydropyranone.

The influence of Lewis acid catalysts on the rates and both regiochemical and stereochemical selectivities of Diels–Alder reactions have been much exploited in synthesis.[1] In general, cycloadditions catalyzed by Lewis acids proceed at significantly lower temperatures and with higher selectivities than their uncatalyzed counterparts.[1,2] Theoretical studies have provided some insight into the mechanism of the Diels–Alder cycloadditions[3] and into the structures of the Lewis acid–carbonyl complexes involved in such reactions.[4] Lewis acids that possess two empty sites of coordination ($SnCl_4$, $TiCl_4$) usually form chelates when a second basic site is present in the carbonyl ligand.[5] In contrast, boron-centered Lewis acids are incapable of chelation.[5,6] The 'chelation control' model has been employed to justify the diastereofacial selectivity in additions to chiral carbonyl and conjugated carbonyl systems.[1,2,5,7]



1a R^1 = $PhCH_2$ (Bn)
b R^1 = 2-(*R*)-octyl

2a R^1 = Bn, R^2 = Me
b R^1 = 2-(*R*)-octyl, R^2 = Me
c R^1 = Bn, R^2 = H

3a R^1 = Bn, R^2 = Me
b R^1 = 2-(*R*)-octyl, R^2 = Me
c R^1 = Bn, R^2 = H

Scheme 1.

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We have recently described a convenient procedure for the synthesis of sugar-derived chiral dihydropyranones, which have proved to be reactive dienophiles in Diels–Alder reactions.[8,9] Such cycloadditions led to optically active adducts with high facial- and *endo*-diastereoselectivities. These dihydropyranones possess a second basic site, an alkoxy group, vicinal to the carbonyl ligand. Therefore, we report here the effect of chelate forming Lewis acids ($SnCl_4$, $TiCl_4$) on the stereochemical course of the cycloaddition.

Boron trifluoride etherate promotes efficiently the Diels–Alder addition of butadienes[8] and cyclic dienes[9] to such dihydropyranones as **1a** (Scheme 1). Thus, under optimized conditions (1 molar equivalent of $Et_2O{\cdot}BF_3$, −18°C, 15 min) the reaction of (2*S*)-2-benzyloxy-2*H*-pyran-3(6*H*)-one (**1a**) with 2,3-dimethylbutadiene afforded a 98:2 ratio of (3*S*,4a*R*,8a*S*)- (**2a**) and (3*S*,4a*S*,8a*R*)-3-benzyloxy-6,7-dimethyl-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (**3a**), named, respectively, as α (**2a**) and β (**3a**) adducts.[10] Similarly, the cycloaddition of **1a** with cyclopentadiene was highly facial (95:5 α:β) and *endo*-diastereoselective (Table 1). Zinc(II) chloride showed a behavior similar to that of $Et_2O{\cdot}BF_3$, and the concentration of both catalysts had only slight influence on the stereochemistry of the addition. In contrast, other Lewis acid catalysts, such as tin(IV) chloride and titanium(IV) chloride strongly influenced the facial selectivities of the cycloadditions, depending upon the concentration of the catalyst employed. Although reactions of **1a** with dienes conducted in the presence of 0.1–0.2 molar equivalents of $SnCl_4$ afforded the α-adducts (**2a** or **4a**) as main products, an increase in the concentration of tin(IV) chloride caused a significant change on the facial stereoselectivity. Thus, with 1 molar equivalent of $SnCl_4$, the diastereoselectivity in the addition of 2,3-dimethylbutadiene to **1a** was reversed in favor of the β-adduct (ratio 24:76 for **2a**:**3a**), whereas almost equal amounts of **4a** and **5a** were obtained for the reaction of **1a** with cyclopentadiene, although the *endo*-selectivity was maintained. A similar trend was observed for cycloadditions of **1a** promoted by $TiCl_4$.

These results suggested that $SnCl_4$ and $TiCl_4$ catalysts induced a change in the direction of attack of the dienes to **1a**, or alternatively, that the catalyst could promote the isomerization of the acetal center (C-3) of adducts **2a** or **4a** to give the enantiomers of **3a** and **5a**, respectively. We have previously reported this type of isomerization for Diels–Alder adducts of **1a** with 1,3-cyclohexadiene.[9] To exclude this possibility, the cycloaddition of **1b** with 2,3-dimethylbutadiene was carried out. As **1b** possesses an additional stereocenter at the C-2 substituent (2-(*R*)-octyl), the adducts **3b** and the one resulting from the isomerization of **2b** should exhibit different physical and spectral properties as they are diastereomeric products. Thus, the $SnCl_4$-promoted cycloaddition from **1b** led to **3b** (major) and **2b** as the only products detected and isolated,[12] hence the isomerization of **2b** was not observed. Furthermore, compounds **2a** and **3a** (or **4a** and **5a**) were stable to exposure to $SnCl_4$ under the conditions employed for the cycloadditions, as they were recovered unchanged (identical spectra and optical rotation) from the respective mixtures.

As isomerization of **2a** and **4a** during the cycloaddition was excluded, stereoelectronic factors operating in the intermediate species generated by interaction of **1a** with the Lewis acids, should be responsible for the observed stereoselectivities. Experiments of ^1H NMR were conducted to detect the formation of complexes between **1a** and Lewis acids. Magnetic resonance spectroscopy has been a valuable tool for determining structures and charge distributions of Lewis acid complexes with carbonyl compounds.[13] Spectra of **1a** in $CDCl_3$ solution were recorded after addition of the Lewis acid.[14] Data

Table 1. Facial selectivities of Diels–Alder reactions of **1a** with dienes under thermal and Lewis-Acids catalyzed conditions[11]

Diene[a] (mol equiv.)	Catalyst (mol equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	dr[c,d] α/β	dr[c,e] *endo*/*exo*
A (3.7)		PhMe	115	90	47	92:8	
A (2.1)	$ZnCl_2$ (2.0)	PhMe	45	7	62	90:10	
A (1.7)	$Et_2O{\cdot}BF_3$ (1.0)	PhMe	−18	15 min	81	98:2	
A (2.6)	$SnCl_4$ (0.15)	PhMe	−18	1	62	95:5	
A (1.7)	$SnCl_4$ (1.0)	PhMe	−18	15 min	79	24:76	
A (2.1)	$SnCl_4$ (1.0)	CH_3CN	−18	30 min	72	95:5	
A (excess)	$TiCl_4$ (1.0)	CH_2Cl_2	−42	30 min	58	34:66	
A (3.5)	$TiCl_4$ (1.0)	CH_2Cl_2/CH_3CN 7:1	−30	30 min	72	95:5	
B (3.4)		PhMe	90	96	79	96:4	91:9
B (2.0)	$Et_2O{\cdot}BF_3$ (1.0)	PhMe	−18	15 min	64	95:5	93:7
B (2.0)	$SnCl_4$ (0.15)	PhMe	−18	30 min	61	81:19	92:8
B (2.0)	$SnCl_4$ (1.0)	PhMe	−18	15 min	64	55:45	93:7

[a] A: 2,3-dimethylbutadiene, B: cyclopentadiene.
[b] Yield of adducts after isolation by flash chromatography.
[c] The diastereomeric ratio (dr) was calculated from the ^1H NMR spectrum of the crude reaction mixture.
[d] Includes the *exo* isomer.
[e] Ratio of α-isomers.

Table 2. Selected ^{1}H NMR spectral data for **1a** recorded in the presence of Lewis acids

Lewis acid added (mol equiv.)	H-5			H-6		H-6′		H-2		H-4	CH_2Ph
	δ (ppm)	$J_{5,6}$	$J_{5,6'}$	δ (ppm)	$J_{4,6}$	δ (ppm)	$J_{4,6'}$	δ (ppm)	$J_{2,4}$	δ (ppm)	δ (ppm)
	7.05	1.8	3.8	4.56	2.5	4.27	1.8	4.96	0.7	6.15	4.85, 4.73
$Et_2O{\cdot}BF_3$ (1.0)	7.15	1.8	3.8	4.56	2.5	4.29	1.7	5.01	0.7	6.23	4.85, 4.73
$SnCl_4$ (0.1)	7.13	2.0	3.7	4.57	2.4	4.31	1.8	5.00	0.6	6.21	4.86, 4.73
$SnCl_4$ ($\sim$0.6)	7.31	2.5	3.1	4.64	2.0	4.40	2.1	5.11	$<$0.5	6.38	5.07, 4.89
$SnCl_4$ (1.0)	7.37	2.6	3.0	4.67	2.0	4.44	2.1	5.13	$<$0.5	6.41	5.10, 4.92
$SnCl_4$ (1.0)[a]	7.27	2.1	3.6	4.62	2.4	4.38	1.8	5.07	0.6	6.34	4.94, 4.80

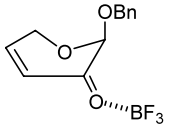
[a] $CDCl_3/CD_3CN$ (9:1) was employed as solvent.

collected in Table 2 show that $Et_2O{\cdot}BF_3$ and $SnCl_4$ caused downfield shift of the resonance of the vinylic H-5, which indicates that a complex involving the carbonyl group of **1a** is formed.[13] Except for the deshielding effect on H-5 (and H-4), the spectra of **1a** recorded with or without $Et_2O{\cdot}BF_3$ were practically identical. This result suggests that coordination of this Lewis acid takes place with the carbonyl oxygen rather than to the other oxygen-coordination sites present in the ligand, as almost no significant shiftings were observed for H-6,6′ and for the methylene protons of the benzyloxy group. Furthermore, the coupling constant values were indicative that, in the presence or absence of $Et_2O{\cdot}BF_3$, the dihydropyranone **1a** adopts the same conformation. The ^2J and ^4J couplings agreed with an E_0 geometry, as their values were similar to those found for levoglucosenone, in which the pyranone is constrained to the E_0 conformation because of the five-membered fused ring.[15] Accordingly, AM1[16] semiempirical molecular orbital calculations (using the MOPAC program) for (*R*)-2-methoxy-2*H*-pyran-3(6*H*)-one (the 2-methoxy analogue of **1a**) predicted the conformer having the methoxy group axially oriented (E_0) to be favored by 12.7 kJ mol^{-1} over its equatorial counterpart (^0E). This conformational preference may be attributed to the anomeric effect, probably intensified by the presence of the adjacent carbonyl group.[17]

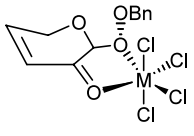
In contrast with the only small changes that the addition of $Et_2O{\cdot}BF_3$ produces on the spectrum of **1a**, progressive variations in chemical shifts and in the magnitude of coupling constants were observed when the ^{1}H NMR spectrum of **1a** was recorded in the presence of increasing concentrations of $SnCl_4$.[14] The coupling constants pattern suggested that, upon complexation, **1a** shifted its conformational equilibrium from the E_0 to the ^0E form. An additional salient feature was the gradual deshielding of the methylene protons of the benzyloxy group, which was indicative of coordination of the benzyloxy oxygen atom to $SnCl_4$. Furthermore, as shown in Table 2, the spectrum of **1a** recorded in the presence of $SnCl_4$ and a donor solvent (e.g. acetonitrile) resembled that of **1a** with $Et_2O{\cdot}BF_3$ in $CDCl_3$ solution. Hence, in the presence of a donor solvent that competes by coordination sites in the Lewis acid,[5,18] complexes of the type of **6** (Scheme 2) seem to prevail. All these results are consistent with the chelation of **1a** by $SnCl_4$. This Lewis acid is able to form six-coordinate octahedral complexes, like **7**, with α-alkoxy carbonyl systems.[19] The formation of the intermediate chelate **7** involving the carbonyl and the vicinal alkoxy group of **1a** seems to induce the conformational inversion of the pyranone ring.

The diastereoselectivity observed for the Lewis acid-promoted cycloadditions of **1a** with dienes may be justified on the basis of steric effects operating in the intermediate complexes. Thus, the facial selectivity in cycloadditions to **6** should be controlled by the sterical hindrance exerted by the axially oriented benzyloxy group over the β face.[10] Chelation of **1a** with $SnCl_4$ promoted a conformational switch that makes both sides of the double bond available for the approach of the dienes. The absence of stereodifferentiation leads to approximately the same amounts of adducts **4a** and **5a**; whereas reverse diastereoselectivity was observed for the formation of **2a** and **3a** (24:76 ratio). As $TiCl_4$, similar to $SnCl_4$, is able to form chelate complexes,[5] both catalysts have a similar influence on the stereochemical course of the reaction.

In summary, the results show that the facial selectivity of the addition of dienes to the dienophilic dihydropyranones derived from pentoses is strongly influenced by the Lewis acid employed as catalyst. Thus, the use of $SnCl_4$ or $TiCl_4$ led to diastereomers that not otherwise can be obtained in preparative scale, in thermally or $Et_2O{\cdot}BF_3$-promoted reactions. As the selectivity also relies upon the configuration of the stereocenter (C-2) of the dihydropyranones, and both *R* and *S* isomers of these compounds are available,[9] the Diels–Alder reactions provide a straightforward access to enantiomers of carbocycles having significant synthetic potentiality.



6



7 (M = Sn, Ti)

Scheme 2.

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10. The α and β descriptors were employed to indicate that the addition of the diene to the (2*S*)-dihydropyranone ring took place from the opposite (α) or the same side (β) respect to the 2-alkoxy substituent.
11. Representative procedure for the Lewis acid-promoted cycloaddition: to a solution of the dienophile **1a** (50 mg, 0.24 mmol; ee >86%) in the anhydrous solvent (0.5 mL) was added the Lewis acid catalyst. The resulting mixture was stirred at −18°C for 10 min, and then the flask was placed in a bath at the temperature desired for the cycloaddition. A solution of the diene in the dry solvent (0.6 mL) was slowly injected under argon, and the temperature was maintained for the time indicated in Table 1. The reaction mixture was diluted with ethyl ether or CH_2Cl_2 (30 mL), and washed with satd aq $NaHCO_3$, satd aq NaCl, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (1–2% EtOAc in hexane) to afford the corresponding cycloadducts (ee >86%). Their yields are reported in Table 1.
12. Cycloadducts **2b** and **3b**: the general procedure for the Lewis acid-promoted cycloaddition was followed starting from **1b** (0.24 g, 1.06 mmol), $SnCl_4$ (0.13 mL, 1.10 mmol) and 2,3-dimethylbutadiene (0.16 g, 1.96 mmol). **2b** (67 mg, 20%); $[\alpha]_D$ −39.7 (*c* 1.1, $CHCl_3$). **3b** (161 mg, 49%); $[\alpha]_D$ −13.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (bs, 1, H-3), 4.01 (dd, 1, $J_{1,1'}=11.4$ Hz, $J_{1,8a}=11.4$ Hz, H-1ax), 3.82 (m, 1, $J=6.1$ Hz, H-2 octyl), 3.58 (dd, 1, $J_{1',8a}=4.6$ Hz, H-1′eq), 2.78 (m, 2, H-4a,5), 2.51 (m, 1, $J_{4a,8a}=7.1$ Hz, $J_{8,8a}\sim J_{8',8a}\sim 4.6$ Hz, H-8a), 2.11 (bd, 1, $J_{8,8'}=19.1$ Hz, H-8), 1.92 (bd, 1, $J_{5,5'}=16.0$ Hz, H-5′), 1.85 (bd, 1, H-8′), 1.63, 1.60 (2 bs, 6, 2 CH_3), 1.50–1.25 (m, 10, CH_2 octyl), 1.15 (d, 3, $J=6.1$ Hz, CH_3-1 octyl), 0.89 (t, 3, $J=6.3$ Hz, CH_3-8 octyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 204.9 (C-4), 122.9, 122.7 (C-6,7), 97.5 (C-3), 73.5 (C-2′), 62.2 (C-1), 45.7, 35.5 (C-4a,8a), 37.2, 32.1, 31.9, 29.2, 28.4, 25.7, 22.6 (C-5,8 and 5 CH_2 octyl), 19.1 (×2), 18.8, 14.1 (4 CH_3). Anal. calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.79; H, 10.67%.
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14. Complexation of **1a** with Lewis acids: for the ^{1}H NMR experiments, the dihydropyranone **1a** (10 mg) was dissolved in $CDCl_3$ (0.6 mL) in a NMR tube and cooled to −78°C. The number of molar equivalents of the Lewis acid indicated in Table 2 were added. The solution was stirred and allowed to reach room temperature to register the spectrum. Compound **1a** was stable at temperatures between −20 and 20°C, for times longer than those required for the acquisition of the spectrum.
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