Regiocontrolled and Stereocontrolled Diels-Alder Cycloadditions of 2-Pyrones and Unactivated, Unbranched 1-Alkenes

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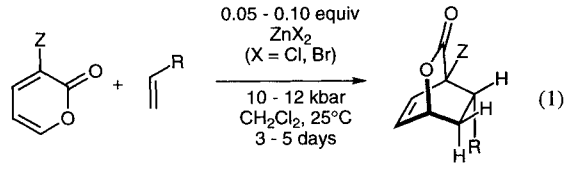
Dedicated to E.J. Corey with admiration and affection

Abstract: The combination of 10-12 kbar pressure plus a catalytic amount of either zinc dibromide or zinc dichloride promotes Diels-Alder cycloadditions of 3-bromo-2-pyrone and of commercial 3-methoxycarbonyl-2-pyrone with several unactivated terminal alkenes, leading regioselectively, stereoselectively and directly to versatile bicyclic lactones.

Inverse-electron-demand Diels-Alder cycloadditions of electron-poor 2-pyrone dienes and electron-rich alkenes have been used extensively in construction of diverse targets and especially of polyfunctionalized aromatic compounds.[2-5] The initial Diels-Alder cycloadducts have been used also, after *in situ* thermal CO_2 extrusion and formation of 1,3-cyclohexadienes, for subsequent intramolecular 4+2-cycloadditions to form efficiently various complex polycyclic structures.[6-8] Apparently no example has been reported, however, of an electron-poor 3-substituted 2-pyrone diene undergoing cycloaddition with an **unactivated** alkene to form an isolable bicyclic lactone cycloadduct.[5,7,9] Because such bicycloadducts would be generally versatile building blocks, we have developed an effective protocol combining a catalytic amount of zinc dichloride or dibromide and 10-12 kbar pressure for regiocontrolled and stereocontrolled 4+2-cycloadditions of 3-bromo-2-pyrone[10] and 3-methoxycarbonyl-2-pyrone with 5 equivalents of various unbranched 1-alkenes to form mainly *syn-endo* racemic bicyclic lactone adducts (±)-**3** (eq. 1). The results are summarized in Table 1.



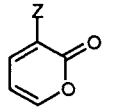
1a, Z = Br
1b, Z = CO_2CH_3

2

(±)-**3**, *syn-endo*
64 - 80%

(1)

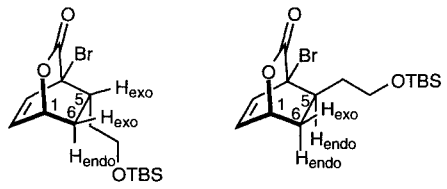
Table 1. Cycloadducts formed via Eq. 1



		3-*syn* (*endo* : *exo*)[a]	**3**-*anti* (*endo* : *exo*)[a]
1a, Z=Br	**2a**, R=$CH_2CH_2CH_3$	99%(3:1)	0%
"	**2b**, R=$CH_2Si(OEt)_3$	80%(>20:1)	16%(>20:1)
"	**2c**, R=CH_2CH_2OTBS	60%(>20:1)	5%(4:1)
"	**2d**, R=$CH_2CH_2OCH_2Ph$	no reaction	
1b, Z=CO_2CH_3	**2e**, R=CH_2OTBS	77%(25:1)[b]	14%(8:1)
"	**2b**, R=$CH_2Si(OEt)_3$	76%*endo*[c] 9%*exo*[c]	0%
"	**2f**, R=CH_2Ph	64%*endo*[c] 13%*exo*[c]	0%

[a] Determined by ^{1}HNMR
[b] Determined by HPLC
[c] Yield of product after purification by column chromatography

Although Diels-Alder cycloadditions of dienes generally and of 2-pyrone dienes specifically have been promoted by various Lewis acids[11] and, separately, by high pressure, **combining** a Lewis acid and high pressure for successful cycloadditions has received only limited attention.[12-14] It should be emphasized that, when high pressure alone was used for 3 days **without** a Lewis acid, alkene **2c** gave only 6% of cycloadduct **3c**, Z=Br, and in only a 3:1 *syn-endo:syn-exo* ratio. Likewise, various Lewis acids **without** high pressure failed to promote cycloaddition. Also a dramatic lack of reactivity was observed when the homoallylic alcohol protecting group was changed to a benzyl ether (**2d**) instead of a non-coordinating[15] *t*-butyldimethylsilyl ether (**2c**); probably the more basic benzyl ether coordinates with the small amount of zinc salt and thereby diverts this Lewis acid away from activating the pyrone diene. Similarly good results were obtained with 0.05 and with 0.10 equivalents of zinc dibromide or zinc dichloride. Assignments of the cycloadducts' structures were achieved, based on well established precedent,[5,16-18] by ^{1}H NMR homo-decoupling experiments, as illustrated here explicitly for cycloadducts **3c**, Z=Br. In this way, both the regiochemistry and the stereochemistry of the cycloadducts were determined.



3c-*syn-endo*

$J_{1,6exo}$ = 4.0 Hz
$J_{1,6endo}$ = 1.2 Hz
$J_{5,6exo}$ = 9.2 Hz
$J_{5,6endo}$ = 3.2 Hz

3c-*syn-exo*

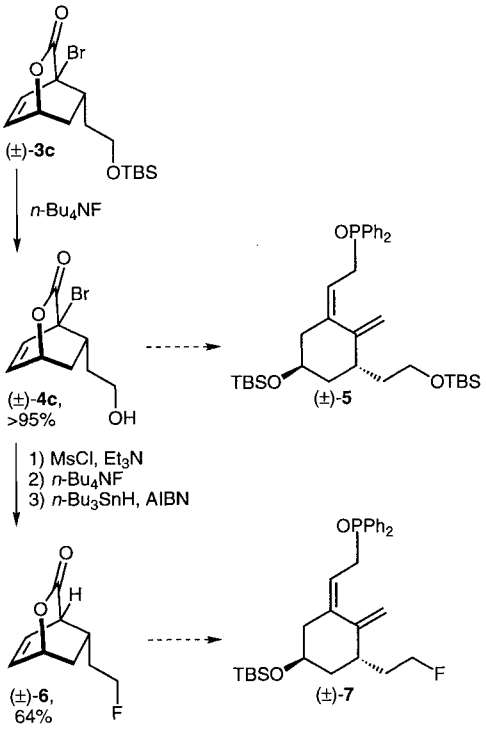
$J_{1,6exo}$ = 4.0 Hz
$J_{1,6endo}$ = 1.6 Hz
$J_{5,6exo}$ = 4.8 Hz
$J_{5,6endo}$ = 10.0 Hz

(TBS = *t*-$BuMe_2Si$)

Using 3-methoxycarbonyl-2-pyrone (**1b**) is even easier than using 3-bromo-2-pyrone (**1a**) because this methyl ester is commercially available. As indicated in Table 1, pyrone ester **1b** also undergoes stereocontrolled 4+2-cycloadditions with both hydrocarbon dienophile **2f** and with oxygen-bearing dienophiles **2b** and **2e** to afford isolable *syn-endo* bicyclic lactone adducts (±)-**3** almost exclusively. As before, ^{1}H NMR homo-decoupling experiments allowed unambiguous assignment of regiochemistry and stereochemistry. On a practical one gram scale, allylic alcohol silyl ether **2e** underwent the cycloaddition shown in Table 1.[19] Various other Lewis acids[11,20,21] including $Sc(OTf)_3$, $YbCl_3$, $Eu(OTf)_3$, $La(OTf)_3$, gave inferior results. For example, $Yb(OTf)_3$[22] and allylic silane **2b** gave cycloadduct **3c**, Z=$COOH_3$, in only 50% yield even though the stereocontrol was a bit better than with $ZnBr_2$. Also, $Pr(hfc)_3$[23] and allylic alcohol silyl ether **2e** gave cycloadduct **3c**, Z=$COOCH_3$, in only a 1:1 *syn-endo:anti-endo* ratio, and this dienophile **2e** with $Yb(OTf)_3$ as Lewis acid and one

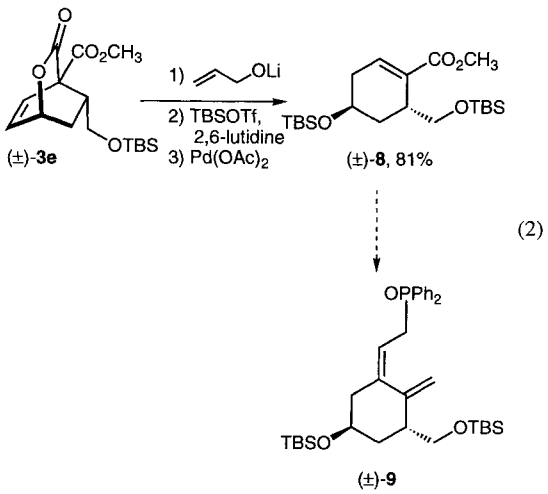
equivalent of the basic additive of 2,6-di-*t*-butylpyridine[24] gave cycloadduct **3e**, Z=$COOCH_3$, in only 39% yield as the *syn-endo* stereoisomer (plus 4% *anti-endo*). Using a full equivalent of zinc dibromide did not give better results than using only 0.05 equivalent. Thus, it appears that zinc dichloride and dibromide catalysts can coordinate with 3-bromo- and 3-methoxycarbonyl-2-pyrones, thereby activating them (increasing their electrophilicity) sufficiently for successful 4+2-cycloaddition with the 1-alkenes reported here. Furthermore, because only 0.05-0.10 equivalents of the zinc dihalides are sufficient to promote these cycloadditons, coordination of the zinc salts to the pyrone reactant must be much stronger than to the bicyclic products. Using 4-cyano-1-butene as dienophile was ineffective, possibly because this unsaturated nitrile competed too successfully with the pyrone for coordination with the Lewis acid.

As an illustration of the synthetic versatility of bicyclic lactone adducts **3**, *syn-endo* silyl ether **3c**, Z=Br, was desilylated to form the corresponding alcohol that we have made previously *via* an independent route and that we have converted into phosphine oxide **5**,[25] the A-ring unit used in a convergent synthesis of cell growth-inhibiting 1-hydroxyethyl analogs of vitamin D_3 (Scheme I).[26] Furthermore, mesylation of alcohol **4c** followed by mesylate displacement by fluoride anion and finally radical-mediated chemospecific replacement of the angular bromine atom by a hydrogen atom produced bicyclic lactone fluoride **6** that we have carried on to vitamin D analog A-ring synthon phosphine oxide **7**.[27] Likewise, as shown in eq. 2, bicycloadduct **3e**, Z=$COOCH_3$, was converted smoothly into cyclohexene **8** that we have prepared indirectly before and that we have converted previously into physiologically potent 1-hydroxymethyl hybrid analogs of vitamin D_3.[28,29]



Scheme 1

In summary, combining 10-12 kbar pressure and a zinc dihalide as a Lewis acid catalyst has allowed successful 4+2-cycloadditions of 3-bromo-2-pyrone and of commercial 3-methoxycarbonyl-2-pyrone with various unactivated terminal alkenes, leading regioselectively, stereoselectively and directly to several synthetically useful *syn-endo* substituted bicyclic lactones. The high regiocontrol in these cycloadditions is understandable based on electronic considerations; the high stereocontrol, however, is hard to rationalize at this time. Further applications of this protocol are being examined.



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19. A typical experimental protocol is as follows:
Preparation of bicyclic lactone 3e (Z = CO_2CH_3): A 5.5 in.
length of 7/8 in. heat-shrinkable teflon tubing (Ace Glass, #12685-40) was sealed on one end with a glass dowel plug. To

the tube were added 3-carbomethoxy-2-pyrone (**1b**, Aldrich, 1 g, 6.48 mmol), zinc bromide (75 mg, 0.33 mmol), dry CH_2Cl_2 (10mL), and alkene **2e** (5.60 g, 32.6 mmol). The open end of the tube was sealed, and the "sealed tube" was pressurized at 10-12 Kbar at room temperature for 3 days. The reaction mixture was concentrated on a rotary evaporator. Column chromatography (20% Et_2O/hexane) afforded **3e** (1.93 g, 5.91 mmol, 91%) as a mixture of *syn-endo, syn-exo, anti-endo, and anti-exo* isomers in the proportions 81.8:3.3:13.2:1.7 (ratio determined by HPLC). Further purification by column chromatography allowed isolation of the *syn-endo* isomer as a pure compound (1.18 g, 3.63 mmol, 56%) Cycloadduct **3e**-*syn-endo*, a white solid, had the following characteristics: mp = 53-55°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (ddd, J = 7.6, 1.4, 1.4 Hz, 1H), 6.50 (dd, J = 7.6, 5.2 Hz, 1H), 5.19 (dddd, J = 5.2, 4.0, 1.4, 1.4 Hz, 1H), 3.88 (s, 3H), 3.41 (AB of ABX, $\Delta\nu_{AB}$ = 16.0 Hz, J_{AB} = 10.0 Hz, 2H), 2.83 (X of ABX, J_{AX} = 6.8 Hz, J_{BX} = 6.8 Hz, J = 9.2, 3.4, 1.2 Hz, 1H), 2.41 (ddd, J = 13.6, 4.0, 9.2 Hz, 1H), 1.40 (ddd, J=13.6, 3.4, 1.4 Hz), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.1, 130.5, 130.4, 74.1, 64.2, 57.2, 52.7, 36.6, 30.0, 25.8, 18.4, -5.5, -5.6; IR (neat) 2957, 2933, 2895, 2860, 1757, 1740, 1471, 1438, 1362, 1285, 1258, 1101, 1070, 909, 840 cm^{-1}; LRMS (CI, NH_3, relative intensity) 344 (M+18, 80), 327(M+1, 100), 225(80); HRMS calculated for M+H = 327.1628, found 327.1624.

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