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Hetero Diels-Alder *vs* Mukaiyama Aldol Pathways in the Reaction of Monoactivated Dienes and Aldehydes. A Lewis Acid Study

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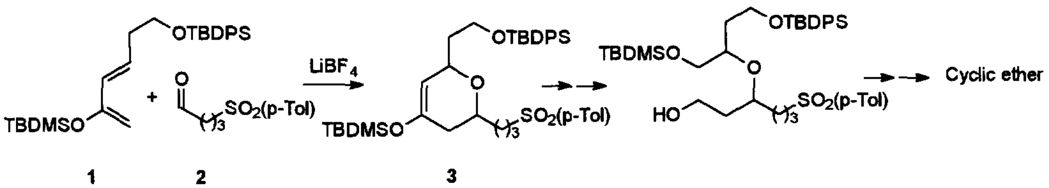
Abstract: The effect of Lewis acid on the reaction of 2-monoactivated dienes and aldehydes was studied searching for more general reaction conditions than those previously published. It was found that $BF_3 \cdot OEt_2$ in diethyl ether gave the best yields of Diels-Alder adducts with good *endo/exo* selectivities. The Mukaiyama aldol-Michael cyclization pathway which has been reported to occur with this Lewis acid in the reaction of diactivated dienes, does not seem to operate with the monoactivated ones. Other Lewis acids gave good yields of silylated aldol products, and a crossover experiment showed that the recently proposed silatropic-ene pathway does not occur under the conditions used.

INTRODUCTION

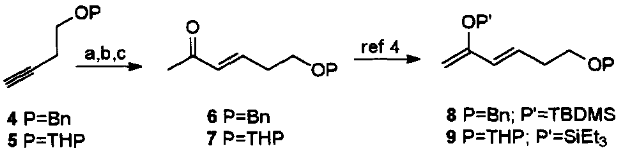
The hetero Diels-Alder reaction[1] of dienes with one activating group at the 2-position and substituted by alkyl groups at the 4-position, with aldehydes under Lewis acid catalysis is a synthetically interesting process, yielding adducts with substituents at the positions α and α' to the oxygen atom of the pyran ring. These compounds can be transformed into linear ethers which in turn can be used in the synthesis of natural products of interest.[2] Based on the work done by Danishefsky and coworkers with monoactivated dienes,[3] we started a project oriented to find new synthetic uses for this reaction, and thus increase its scope. During the course of our work, we found that the conditions described in Danishefsky's work ($MgBr_2$/THF; $ZnCl_2$/THF; $Yb(fod)_3/CHCl_3$) were not generally applicable, since the reaction outcome is heavily dependent on the structure of the reactants. Thus, small changes in the structure of the dienes (shortening of the side chain or change of the protecting group) resulted in decreased reactivity, even to the point of no reaction under the conditions employed in their work. In a previous communication[2a] we reported the reaction of diene **1** with aldehyde **2** (Scheme 1), but since the reaction conditions used ($LiBF_4/CH_3CN$-C_6H_6) did not work with other combinations of diene and aldehyde, we felt that it would be of interest to find a more general set of conditions.



Scheme 1

RESULTS AND DISCUSION

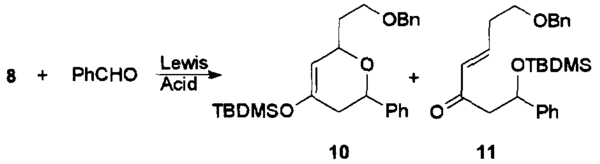
In order to achieve this goal, we started by exploring the reactivity of diene **8** with benzaldehyde (eq 1). Diene **8** was chosen because of its facile preparation (Scheme 2), and its low reactivity under the conditions reported in Danishefsky's work were used.



(a) n-BuLi, THF, -78°C, CH_3CHO; (b) $LiAlH_4$, THF, reflux; (c) Swern oxidation

Scheme 2

tert-Butyldimethylsilyloxy was selected as the activating group instead trimethylsilyloxy, which in principle would give higher reactivity due to steric reasons, because the latter proved to be too unstable under the reaction conditions, decomposing to the corresponding α,β unsaturated ketone **6**, and also because it has been proposed that diactivated dienes bearing the tert-butyldimethylsilyloxy group react through a more pericyclic pathway than those activated by the trimethylsilyloxy group.[5] The results of this study are summarized in Table 1. In all the reactions the rest of the yield is accounted for by the α,β unsaturated ketone **6** formed from the diene, and in some cases for unreacted material.



(1)

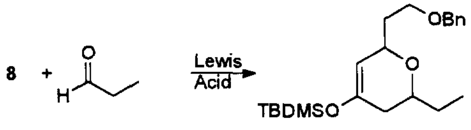
Table 1. Reaction of Diene 8 With Benzaldehyde Under Lewis Acid Catalysis.

Lewis acid	equiv of aldehyde/acid[a]	solvent	temp (°C)	time (min)	yield of **10**[b],% (*cis*:*trans*)[c]	yield of **11**[b], %
Et_2AlCl	1.1/1	CH_2Cl_2	-70	<5	15 (8:1)	55
Et_2AlCl	1.1/1	hexane	-70	30	67 (8.5:1)	3
Et_2AlCl	1.1/1	Et_2O	-78	30	28 (25:1)	42
$BF_3 \cdot Et_2O$	1.5/0.5	hexane	-78	<5	26 (7:1)	40
$BF_3 \cdot Et_2O$	1.5/1	Et_2O	-78	<5	86 (6:1)	<4
$Eu(fod)_3$	1/0.05	CH_2Cl_2	20	4 days	40 (32:1)	-
$LiBF_4$	1.1/1.1	CH_3CN/C_6H_6	20	20	84 (6:1)	-[d]
$AlCl_3$	1.1/0.2	CH_2Cl_2	-78	<5	-	83
$ZnCl_2$	2/2	CH_2Cl_2	20	<5	-	90
$TiCl_4$	1.5/0.05	CH_2Cl_2	-78	<5	-	90

[a] Equivalents relative to diene 8. [b] Isolated yields. [c] Ratio determined by ^1H-NMR or HPLC. [d] Small amounts (<4%) of desilylated aldol were observed.

It can be observed that depending on the Lewis acid and the reaction conditions used, the reaction yields either silylenolpyran **10**, silyl-protected aldol products **11**, or a mixture of both (eq 1). The ratio of the products formed in the reaction depends not only on the Lewis acid used, but also on the solvent employed, and thus when boron trifluoride etherate in diethyl ether, which acts as a relatively mild Lewis acid,[6] is used, silylenolpyran (**10**) were obtained in good yield, and with a 6:1 selectivity favoring the product formed by *endo* approach (cis-adduct). These products can be readily separated by HPLC and the relative stereochemistry determined by NMR experiments.[7] Only very small amounts of aldols were observed under these conditions. When the solvent was changed to hexane the ratio of products changed, favoring the aldol products, whereas with CH_2Cl_2 as solvent a mixture of both types of compounds plus the desilylated derivatives was obtained in a very fast reaction. With Et_2AlCl, the role of the solvent is also important, since changing from CH_2Cl_2 to hexane or diethyl ether the proportion of products changes in the opposite sense to that observed with $BF_3{\cdot}OEt_2$. The best selectivity in hetero Diels-Alder products was obtained when $Eu(fod)_3$ was used as the Lewis acid, but the reaction was very slow and the yield was not very high. The rest of the conditions employed gave similar ratios of *endo:exo* products or good yields of aldols.

$LiBF_4$ gave good yields of Diels-Alder adducts when benzaldehyde or aldehyde **2** was used.[2] With other aldehydes, however, the yields were low. With propionaldehyde the reactivity decreases although it follows the same trend as with benzaldehyde when different Lewis acids are used, $BF_3{\cdot}OEt_2$ giving the best yield of hetero Diels-Alder adducts (**12**) (93%, 2.6:1 *endo:exo*).

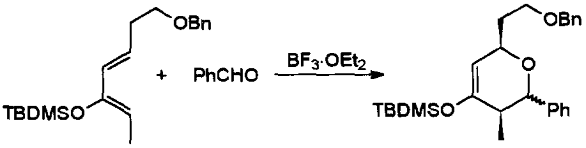


12

(2)

In this case, it is necessary to add the Lewis acid to the aldehyde and wait several minutes before adding the diene in order for the reaction to work with high yield, whereas with benzaldehyde the reaction is fast enough to allow the Lewis acid to be added to a mixture of diene and aldehyde. $BF_3{\cdot}OEt_2$ also worked well with other aldehydes, and thus when diene **1** and aldehyde **2** were allowed to react under $BF_3{\cdot}OEt_2$ catalysis, only **3** was detected as a 2:1 mixture of *endo:exo* isomers, in 77 % yield. It is also of interest that the Mukaiyama aldol reaction takes place readily with certain Lewis acids, when benzaldehyde is used, whereas with other aldehydes only hetero Diels-Alder or decomposition takes place under the same conditions. From these results, Et_2AlCl and $BF_3{\cdot}OEt_2$ showed promise as general Lewis acids for the hetero Diels-Alder reaction of 2-monoactivated dienes with aldehydes.

Danishefsky has reported in his extensive exploration of the use of $BF_3{\cdot}OEt_2$ with diactivated dienes[8] that with this Lewis acid, the process can take place through a tandem aldol addition-Michael reaction with the intermediacy of a siloxonium species which can yield the final product without the loss of the silyl protecting group. In order to check whether this is the case for our system or a pericyclic reaction is involved, diene **13** was prepared stereoselectively with the 2-*Z* configuration, in the same way as **8** (Scheme 2), using propionaldehyde instead of acetaldehyde as starting material, and lithium 2,2,6,6-tetramethylpiperidide/TBDMSOTf for the formation of the dienolsilane, since the use of other procedures or less hindered bases led to mixtures of *E* and *Z* dienes. In the reaction of **13** with benzaldehyde under $BF_3{\cdot}OEt_2$ catalysis, if the first step is an aldol process, two (racemic) compounds can be obtained, each of which can in turn result in two diastereoisomers after the Michael addition step. When the reaction was carried out, only two of the four possible compounds were obtained in a 79% yield and a 8:1 ratio. The spectroscopic data revealed that both were silylenolpyranes, and a combined molecular mechanics[9]-coupling constant study of all possible isomers together with the results of the nOe spectroscopy allowed us to establish the relative stereochemistry of both compounds (eq 3). The result of that study indicated that the stereochemistry of the isolated compounds, **14** and **15**, was consistent with the result of a cycloaddition reaction, with the major product (**14**) corresponding to *endo* approach of the dienophile. Thus, $BF_3{\cdot}OEt_2$ in diethyl ether emerges as the Lewis acid of choice for the hetero Diels-Alder reaction of 2-monoactivated dienes with aldehydes.



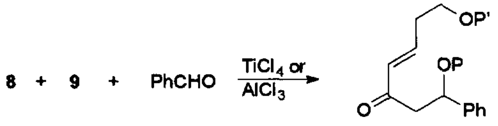
(3)

13

14 β-Ph
15 α-Ph

A number of the Lewis acids employed in this work gave high yields of silylated aldol products. The formation of this type of compounds when attempting to carry out a hetero Diels-Alder reaction has been reported previously,[10] and has been referred to as a group transfer reaction. It has also been proposed recently that the Mukaiyama aldol reaction of enolsilanes and aldehydes under Lewis acid catalysis can, in certain circumstances, proceed via a pericyclic silatropic ene mechanism.[11] In our study the reactions yielding silylated aldol products are quite fast (typically less than 5 minutes), and even after one minute of reaction, no deprotected aldol products were observed (tlc or nmr). Our results using $TiCl_4$ are different from those reported by Reetz and coworkers,[12] since we found that the final product was always a silyl-protected aldol. For this reason, we decided to carry out a crossover experiment similar to the one reported by Mikami and Matsukawa[11] in order to find out whether the process was an inter- or intramolecular one.

When diene **9**, prepared using the procedure described in Scheme 2, was reacted with benzaldehyde in the presence of either $TiCl_4$ or $AlCl_3$, only the corresponding silylated aldol **16** was observed. However, when a mixture of **9** and **8**, which yields exclusively **11** under the same conditions, was added to a solution of Lewis acid and benzaldehyde in CH_2Cl_2 (eq 4), a mixture of equal proportions of the four possible silylated aldols (**11**,**16**,**17** and **18**) was obtained in high yield (85%). To check whether there was any scrambling of the silicon protecting groups on the final aldols, a mixture of **11** and **16** was treated with either Lewis acid under the conditions of the reaction. Both compounds were recovered unaltered, indicating that the scrambling took place during the Mukaiyama aldol reaction, which is consistent with the open-chain mechanism deduced by Reetz using nmr rapid injection techniques,[12] with the difference being that in our case, even when $TiCl_4$ is used, the silicon atom is trapped by the aldol later in the reaction.



(4)

11 P=TBDMS; P'=OBn
16 P=Et_3Si; P'=THP
17 P=TBDMS; P'=THP
18 P=Et_3Si; P'=OBn

In conclusion, it is possible to carry out hetero Diels-Alder reactions of monoactivated dienes and aldehydes, under conditions mild enough to allow for the isolation of the silylenolpyranes, using $BF_3{\cdot}OEt_2$ in diethyl ether as the Lewis acid. The competing Mukaiyama aldol reaction seems to occur via an open-chain mechanism, and not via a silatropic-ene one as reported recently for other uncatalysed and catalysed aldol reactions.

EXPERIMENTAL

General.

Solvents used were purified and dried by the standard procedures before use. The aldehydes were distilled immediately before use. All reactions were performed under argon in oven dried glassware. ^1H-NMR spectra were recorded at 400 MHz, and ^{13}C-NMR at 100 MHz. Flash-column chromatography was performed using silica gel 60 (230-400 mesh). HPLC was performed using a μ-Porasil column (300 × 7.8 mm i.d.) and n-hexane-EtOAc solvent systems.

*Reactions of diene **8** with benzaldehyde under $BF_3{\cdot}Et_2O$ catalysis*

Boron trifluoride etherate (0.1 mL of a 1.38M solution in dry ether) was added under argon to a solution of benzaldehyde (21 μL, 0.21 mmol) and diene **8** (43.8 mg, 0.138 mmol) in 2 mL of ether at -78°C. After 1 min, triethylamine (1 drop) was added and the mixture was stirred for five min and then extracted with ether (3×). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (3% EtOAc/hexanes) gave 50 mg (86%) of **10** as a 6:1 mixture of isomers, which were separated by HPLC (5% EtOAc/hexane).

(2R*, 6R*)-6-[(2'-Benzyloxy)ethyl]-4-(tert-butyldimethylsilyloxy)-2-phenyl-2,3-dihydro-6H-pyran (cis-**10**).

^1H NMR (C_6D_6) δ 7.12 -7.40 (m, 10 H), 4.99 (bs, 1 H), 4.57 (m, 2 H), 4.39 (s, 2 H), 3.77 (m, 1 H), 3.66 (m, 1 H), 2.43 (m, 1 H), 2.23 (ddd, *J*=16.4, 2.9, 2.9 Hz, 1 H), 2.06 (ddd, *J*=6.4, 6.4, 6.4, Hz, 2 H), 1.02 (s, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (C_6D_6) δ 149.1, 143.1, 139.4, 128.5, 127.7, 127.5, 127.4, 126.0, 106.7, 76.1, 73.1, 72.3, 67.1, 38.8, 37.4, 25.8, 18.2, -4.2, -4.5; MS (EI) *m/z* (rel intensity): 424 (M^+,1), 367 (2), 91(100). (Found: 367.17303; calc. for $C_{22}H_{27}O_3Si$: 367.17295).

(2R, 6S*)-6-[(2'-Benzyloxy)ethyl]-4-(tert-butyldimethylsilyloxy)-2-phenyl-2,3-dihydro-6H-pyran (trans -10).*

^1H NMR (C_6D_6) δ 7.13-7.45 (m, 10 H), 4.98 (bs, 1 H), 4.78 (m, 2 H), 4.35 (s, 2 H), 3.63 (m, 1 H), 3.50 (m, 1 H), 2.45 (ddd, *J*=16.5, 9.5, 1.9 Hz, 1 H), 2.27 (dd, *J*=16.5, 3.7 Hz, 1 H), 2.02 (m, 1 H), 1.85 (m, 1 H), 1.02 (s, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (C_6D_6) δ 148.5, 142.8, 139.4, 128.5, 128.4, 127.5, 126.4, 106.3, 73.1, 70.2, 70.0, 67.4, 37.9, 35.4, 25.8, 18.2, -4.3, -4.5.

Eu(fod)$_3$ catalysis.

A solution of benzaldehyde (64 μL, 0.63 mmol), diene **8** (200 mg, 0.63 mmol) and Eu(fod)$_3$ (32.7 mg, 0.032 mmol) in 5 mL of CH_2Cl_2 was allowed to stand at room temperature for 4 days. After extraction with ether and flash chromatography (3% EtOAc/hexane), **10** was obtained as a mixture (106 mg, 40%) in a 32:1 (cis:trans) ratio (^1H NMR analysis).

$LiBF_4$ catalysis.

To a solution of benzaldehyde (35 μL, 0.35 mmol) in dry benzene (2 mL) at 0°C under argon was added $LiBF_4$ (0.35 mL of a 1M solution in CH_3CN). The stirred reaction was allowed to warm to room temperature, and after 15 min a solution of diene **8** (98.6 mg, 0.31 mmol) in dry benzene (1 mL) was added. After 20 min, the solution was poured into a saturated aqueous $NaHCO_3$, and extracted with ether (3×). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography gave 110 mg of **10** (84%) as a 6:1 mixture of cis:trans isomers (^1H NMR analysis), which were separated by HPLC.

$ZnCl_2$ catalysis.

Benzaldehyde (39 μL, 0.39 mmol) was added to a solution of freshly fused zinc chloride (53 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at 0° C under argon. After 15 min at room temperature, the diene **8** (63 mg, 0.2 mmol) was added. After 3 min, triethylamine (2 drops) and water were added. The solution was extracted with CH_2Cl_2 (3×), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/hexanes) gave 76 mg (90%) of **11**, as a colorless oil.

(E)-7-Benzyloxy-1-(tert-butyldimethylsilyloxy)-1-phenyl-4-hepten-3-one (11).

^1H NMR ($CDCl_3$) δ 7.23-7.38 (m, 10 H), 6.84 (dt, *J*=16, 6.8 Hz, 1 H), 6.17 (d, *J*=16 Hz, 1 H), 5.23 (dd, *J*=8.7, 4 Hz, 1 H), 4.52 (s, 2 H), 3.58 (t, *J*=6.5 Hz, 2 H), 3.11 (dd, *J*=14.8, 8.7 Hz, 1 H), 2.63 (dd, *J*=14.8, 4 Hz, 1 H), 2.52 (ddt, *J*=6.8, 6.5 Hz, 2 H), 0.84 (s, 9 H), 0.02 (s, 3H), -0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.4, 144.7, 144.4, 138.0, 132.7, 128.4, 128.2, 127.6, 127.2, 125.7, 73.0, 72.1, 68.2, 50.9, 32.9, 25.7, 18.0, -4.8, -5.2; MS (EI) *m/z* (rel intensity): 424 (M^+, 1), 91 (100). (Found: 367.17121; calc for $C_{22}H_{27}O_3Si$: 367.17295).

$AlCl_3$ catalysis.

To a solution of $AlCl_3$ (8.4 mg, 0.063 mmol) in CH_2Cl_2 (2 mL) at -78°C under argon, was added benzaldehyde (35 μL, 0.347 mmol), and after 15 min, a solution of diene **8** (98 mg, 0.31 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 5 min, quenched by the addition of saturated solution of $NaHCO_3$ and then poured into a solution of potassium sodium tartrate. After extraction with ether (3×), the organic layer was washed with brine, dried ($MgSO_4$), concentrated in vacuo and purified by flash chromatography yielding 109 mg (83%) of **11**.

$TiCl_4$ catalysis.

A solution of benzaldehyde (21μL, 0.21 mmol) and diene **8** (45 mg, 0.142 mmol) in CH_2Cl_2 (2 mL) was cooled at -78° C under argon. To this solution, $TiCl_4$ (0.1 mL of a 0.071 M solution in CH_2Cl_2) was added. After 3 min, the reaction was quenched by addition of saturated solution of sodium acetate (1-2 mL). Workup and flash chromatography yielded 54.2 mg (90%) of **11**.

*Reaction of diene **8** with propionaldehyde.*

To a solution of 39 μL of $BF_3 \cdot OEt_2$ (0.3 mmol) in 2 mL of ether at -50°C were added 22 μL of propionaldehyde (0.3 mmol). After 20 min, diene **8**, (95 mg, 0.3 mmol) in 1 mL of ether was added. The reaction was stirred for 10 min and then quenched as described above for the reaction of **8** with benzaldehyde, yielding 105 mg of **12** (93%) as a 2.65:1 mixture of cis:trans isomers.

(2R, 6R*)-6-[(2'-Benzyloxy)ethyl]-4-(tert-butyldimethylsilyloxy)-2-propyl-2,3-dihydro-6H-pyran (cis -12).*

^{1}H NMR (C_6D_6) δ 7.35-7.13 (m, 5 H), 4.95 (bs, 1 H), 4.42 (m, 1 H), 4.40 (s, 2H), 3.73 (m, 1 H), 3.64 (m, 1H), 3.40 (m, 1 H), 2.11 (m, 1 H), 1.98 (ddd, *J*=6.4, 6.3, 6.3 Hz, 2 H), 1.90 (br d, *J*=16.4 Hz, 1 H), 1.63 (m, 1 H), 1.43 (m, 1H), 1.03 (s, 9 H), 0.95 (t, *J*=7.5 Hz, 3 H), 0.19 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (C_6D_6) δ 149.0, 139.2, 128.2, 127.8, 127.6, 127.4, 127.2, 106.6, 75.4, 72.8, 71.6, 67.0, 37.1, 36.1, 28.9, 25.6, 17.9, 9.8, -4.4, -4.7; MS (EI) *m/z* (rel intensity): 375 (M^+-1, 1), 91 (100).

(2R, 6S*)-6-[(2'-Benzyloxy)ethyl]-4-(tert-butyldimethylsilyloxy)-2-propyl-2,3-dihydro-6H-pyran (trans-12).*

^{1}H NMR (C_6D_6) δ 7.37-7.13 (m, 5 H), 4.92 (bs, 1 H), 4.64 (m, 1 H), 4.42 (s, 2 H), 3.67 (m, 1 H), 3.58

(m, 2H), 2.02 (m, 3 H), 1.80 (m, 1 H), 1.63 (m, 1 H), 1.39 (m, 1 H), 1.03 (s, 9 H), 0.95 (t, *J*=7.4 Hz, 3 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (C_6D_6) δ 148.2, 139.2, 128.2, 127.9, 127.6, 127.2, 106.0, 72.9, 69.4, 68.8, 67.3, 35.8, 35.3, 28.2, 25.6, 17.9, 10.0, -4.5, -4.7; MS (EI) m/z (rel intensity): 376 (M^+, 1), 117(74), 75 (100).

Preparation of (2Z, 4E)-7-Benzyloxy-3-tert-butyldimethylsilyloxy-2,4-heptadiene (13).

To a solution of 84 mg (0.39 mmol) of (*E*)-7-benzyloxy-4-hepten-3-one in 4 mL of THF were added 0.12 mL of *tert*-butyldimethylsilyl-trifluoromethanesulfonate (0.46 mmol). After cooling to -78°C, 1.28 mL of 2,2,6,6-lithium tetramethylpiperidine (0.3 M in THF) were added. After 15 min a satured solution of NH_4Cl was added and the reaction was extracted with ether. The combined organic extracts were dried over $MgSO_4$, the solvent evaporated under vacuum, and the crude mixture purified by flash chromatography (2% EtOAc/hexanes), yielding 124 mg (97%) of diene **13** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.28-7.36 (m, 5H), 5.94 (d, *J*=15.5 Hz, 1H), 5.80 (dt, *J*=15.5, 6.9 Hz, 1H), 4.78 (q, *J*= 7.0 Hz, 2H), 4.53 (s, 2H), 3.54 (t, *J*=6.8 Hz, 2H), 2.42 (dt, *J*=6.8, 6.9 Hz, 2H), 1.65 (d, *J*=7.0 Hz, 3H), 1.03 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.9, 138.4, 130.4, 128.3, 127.6, 127.4, 124.7, 108.0, 72.9, 70.1, 40.7, 32.7, 26.0, 18.4, 11.7, -3.7, -4.5; MS (E/I) m/z (rel intensity): 332 (M+, 1), 91 (100).

Reaction of diene 13 with benzaldehyde under $BF_3{\cdot}OEt_2$ catalysis.

The same procedure described before for the reaction of **8** with benzaldehyde was used. Starting from 94 mg of **13** (0.28 mmol), 1 equiv of benzaldehyde and 1 equiv of $BF_3{\cdot}OEt_2$, 98 mg (79%) of a mixture of **14** and **15** in a 8:1 ratio were obtained.

(2R, 3R*, 6R*)-6-(2'Benzyloxy)ethyl-4-(tert-butyldimethylsilyloxy)-3-methyl-2-phenyl-2,3-dihydro-6H-pyran (14).*

^{1}H NMR (C_6D_6) δ 7.38-7.15 (m, 10 H), 4.85 (bs, 1 H), 4.78 (d, *J*=2.7 Hz, 1 H), 4.54 (m, 1 H), 4.43 (s, 2 H), 3.81 (m, 1 H), 3.71 (m, 1H), 2.32 (m, 1 H), 2.05 (m, 2 H), 1.04 (s, 9 H), 0.99 (d, *J*=7 Hz, 3 H), 0.22 (s, 3 H), 0.19 (s, 3 H). ^{13}C NMR (C_6D_6) δ 154.1, 141.0, 139.1, 128.2, 127.2, 126.6, 125.7, 104.5, 77.9, 72.9, 72.1, 67.0, 39.9, 37.2, 25.6, 17.9, 12.7, -4.2, -5.0; MS (EI) m/z (rel intensity): 438 (M^+, 0.3), 381 (13), 91 (100).

(2S, 3R*, 6R*)-6-(2'Benzyloxy)ethyl-4-(tert-butyldimethylsilyloxy)-3-methyl-2-phenyl-2,3-dihydro-6H-pyran (15).*

^{1}H NMR (C_6D_6) δ 7.46-7.11 (m, 10 H), 4.93 (s, 1 H), 4.66 (m, 1 H), 4.45 (d, *J*=7.3 Hz, 1 H), 4.31 (bs, 2 H), 3.60 (m, 1 H), 3.52 (m, 1H), 2.60 (m, 1 H), 2.09 (m, 1 H), 1.88 (m, 1 H), 1.11 (d, *J*=6.1 Hz, 3 H), 1.03 (s, 9 H), 0.20 (s, 3 H), 0.19 (s, 3 H); ^{13}C NMR (C_6D_6) δ 151.8, 141.4, 139.2, 128.2, 128.1, 127.8, 127.6, 105.2, 78.0, 72.8, 69.3, 67.2, 39.3, 35.4, 25.6, 18.0, 14.3, -4.6, -4.7; MS (EI) m/z (rel intensity): 438 (M^+, 1), 381 (32), 303 (100).

(E)-1-Phenyl-7-(2'-tetrahydropyranyloxy)-1-triethysilyloxy-hept-4-en-3-one (16).

The same procedure as described above for the preparation of **11** was followed with either $AlCl_3$ or $TiCl_4$ as the Lewis acid. In both cases, **16** was obtained as a colorless oil which was purified by HPLC (5 % EtOAc/hexanes). From 50 mg of **9** (0.16 mmol), 16 μL of benzaldehyde (0.16 mmol) and 10.7 mg of $AlCl_3$ (0.08 mmol), 58.9 (88%) of **16** were obtained.

^{1}H-NMR ($CDCl_3$) δ 7.20-7.36 (m, 5 H), 6.82 (dt, *J*=16, 6.8 Hz, 1 H), 6.15 (d, *J*=16 Hz, 1 H), 5.22 (dd, *J*=8.4, 4.3 Hz, 1 H), 4.58 (bs, 1 H), 3.82 (m, 2 H), 3.49 (m, 2 H), 3.09 (dd, *J*=15, 8.4 Hz, 1 H), 2.65 (dd, *J*=15, 4.3 Hz, 1 H), 2.48 (dt, *J*=6.8, 5.5 Hz, 2H), 1.5-1.82 (m, 6 H), 0.82 (t, *J*=7.9 Hz, 9 H), 0.48 (m, 6 H); ^{13}C-NMR ($CDCl_3$) δ 198.3, 144.8, 144.5, 132.6, 128.2, 127.2, 125.7, 98.8, 71.6, 65.5, 62.3, 51.0, 32.9, 30.5, 25.4, 19.4, 6.6, 4.6.

Crossover experiment.

The same procedure described for the preparation of **11** was used. Starting from 21.1 mg (0.16 mmol) of $AlCl_3$, 32 μL of benzaldehyde (0.32 mmol), 50 mg of diene **8** (0.157 mmol) and 50 mg of diene **9** (0.16 mmol) in CH_2Cl_2, 140 mg of crude reaction products were obtained, which were purified by HPLC (5% EtOAc/hexanes). Two peaks in a 1:1 ratio were separated. ^{1}H-NMR analysis revealed that the less polar peak contained a 1:1 mixture of **11** and **18** and the more polar peak a 1:1 mixture of **16** and **17**. The overall isolated yield was 85%.

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