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# Hetero-Diels—Alder reaction of aromatic aldehydes catalyzed by titanium tetrachloride: computational and experimental results

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#### ABSTRACT

Computational calculations of the hetero-Diels–Alder (HDA) reactions of benzaldehyde with 2,3dimethyl-1,3-butadiene (DMB) catalyzed by BF<sub>3</sub>, EtAlCl<sub>2</sub> or TiCl<sub>4</sub> at the density functional theory (DFT) (B3LYP/6-31G(d,p)) level reveal that the reactions involve activation energy barriers of 14.59, 14.34, and 17.44 kcal mol<sup>-1</sup>, respectively. In the first two cases, reaction occurs through a concerted mechanism, whereas in the presence of TiCl<sub>4</sub>, stepwise mechanism involving zwitterionic intermediate is followed. The reaction with isoprene proceeds with complete regioselectivity leading to the expected regiosomer having O/Me in 1:4 positions. The computational results have been verified experimentally when aromatic aldehydes react with 1,3-dienes in the presence of a catalyst to give 3,6-dihydro-2H-pyran derivatives in high yields.

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#### 1. Introduction

Since its discovery in 1928, the Diels–Alder (DA) reaction<sup>1</sup> has witnessed many path-breaking developments<sup>2</sup> resulting in innumerable elegantly planned applications in the construction of many complex organic molecules.<sup>3</sup> The scope of the DA reaction was greatly broadened by using hetero-dienes and heterodienophiles facilitating the synthesis of many heterocycles and complex natural products.<sup>4</sup> Hetero-Diels–Alder (HDA) reaction using carbonyl compounds as hetero-dienophiles or hetero-dienes has made a wide variety of substituted dihydropyrans accessible, which occur as structural motifs in many biologically active natural products.<sup>4,5</sup> However, carbonyl compounds as dienophiles are much less reactive and the HDA reaction between aldehydes and dienes has been limited either to the reaction of highly electronrich dienes (such as Danishefsky's diene) with simple aldehydes or to the reaction of highly activated aldehydes (such as chloral and glyoxalates) with simple dienes.<sup>6</sup> In view of this, the HDA reaction of the carbonyl compounds often requires a Lewis acid as catalyst. For example, aldehydes underwent HDA reaction with Danishefsky's diene in the presence of Lewis acid catalysts.<sup>7</sup> The HDA reaction of simple dienes, such as cyclohexadiene and dimethylbutadiene (DMB) have been accomplished with alkyl glyoxalates in the presence of cationic copper-Lewis acid catalyst.<sup>8</sup> The

HDA reaction of unactivated aldehydes with simple dienes was achieved in the presence of  $Pd^{+2}$  catalyst<sup>9a</sup> or a mixture of AlCl<sub>3</sub> or SnCl<sub>4</sub> with nitroalkane as catalyst.<sup>9b</sup> Similarly in other cases, strong Brönsted acid was used as catalyst, which caused side reactions or gave poor yields.<sup>9c,d</sup>

The experimental results of the DA reactions, particularly the observed stereo- and regio-selectivities, have been often rationalized on the basis of computational calculations.<sup>10</sup> Likewise, theoretical studies of the HDA reactions have been carried out, though to a lesser extent, to investigate their mechanism and mode of action of the catalyst.<sup>11</sup> For example, in a study on the mechanism of the HDA reactions with Danishefsky's diene at the semiempirical (AM1) and ab initio (HF/6-31G) levels, the uncatalyzed reaction was found to proceed through a concerted mechanism involving an asynchronous transition state, whereas, in the presence of (MeO)<sub>2</sub>AlMe as catalyst, the reaction occurred via a stepwise mechanism involving a zwitterionic intermediate.<sup>11a</sup> Theoretical study of the mechanism of the HDA reaction of butadiene with benzaldehvde catalyzed by chiral N.N'-dioxide/In(OTf)<sub>3</sub> complex by using DFT method indicated that the catalyzed reaction proceeded through a concerted mechanism via a highly zwitterionic transition state and the lowest energy barrier was 11.8 kJ mol<sup>-1</sup>, 63.0 kJ mol<sup>-1</sup> lower than that of the uncatalyzed reaction. Furthermore, the endo approach was found to be preferred over the exo approach, because the latter suffered from more steric hindrance.<sup>12</sup> In another theoretical investigation at the DFT level, intramolecular HDA reaction of cyclic benzylidene sulfoxides was predicted to give endo products stereoselectively, which accorded well with the experimental results.<sup>11c</sup> The





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stereoselectivity in the HDA reaction of *ortho*-xylylenes with acetaldehydes was investigated theoretically with the B3LYP and MP2 functionals and the observed high *endo* selectivity was shown to result from the CH $-\pi$  interactions between the alkyl groups of the aldehyde and the aromatic ring in the transition state.<sup>13</sup>

We undertook a systematic theoretical and experimental investigation of the HDA reactions of aromatic aldehydes with simple dienes, namely DMB and isoprene; the results are presented here.

#### 2. Results and discussion

#### 2.1. Computational results

To investigate the mechanisms of the HDA reactions of the aromatic aldehydes in the absence of the catalyst and also in the presence of three catalysts, we computed fifteen model reactions (Scheme 1 and Table 1) at the DFT level.



Scheme 1. Computed model DA reactions of aromatic aldehydes.

In a theoretical study of the complexes of formaldehyde with titanium tetrachloride at the ab initio level, formation of the 1:1 and 2:1 complexes was detected and the latter was found to be energetically preferred.<sup>14</sup> In view of this, we also optimized 1:1 and 2:1 complexes of benzaldehyde with titanium tetrachloride and determined their energies. It is found that the 2:1 complex is more stable than the 1:1 complex by ca. 11 kcal  $mol^{-1}$ . For the purpose of the calculation of the activation enthalpies, however, 1:1 complexes were taken into account. Furthermore, on attempting to optimize the transition structures corresponding to the endo and the exo approaches in the HDA reaction of benzaldehyde-TiCl<sub>4</sub> complex with DMB, only the former was optimized, whereas the transition structure for the exo approach suffered from the steric hindrance between the diene moiety and TiCl<sub>4</sub> and optimization could not be completed. This observation is similar to the one reported for the HDA reaction of benzaldehyde with butadiene catalyzed by In(III) complex.<sup>12</sup> In view of this, in other cases, the transition structures for the endo approach only were investigated.

*2.1.1. Geometries.* The B3LYP/6-31G(d,p) optimized geometries of the transition structures, **TS1–6** involved in the uncatalyzed HDA reaction nos, 1–7 are shown (Fig. 1).

In accordance with the earlier report,<sup>10a</sup> uncatalyzed HDA reactions in the present case also follow pericyclic mechanism involving concerted transition structures that are, however, asynchronous, formation of the C–C bond (WBI=0.45–0.48) being more advanced than the C–O bond (WBI=0.33–0.36), in the *endo* approach of the diene. Asynchronous transition structures have been located in the dimerization of methacrolein, which have been attributed to the merging of [4+2] and [2+2] mechanisms.<sup>15</sup> It is noteworthy that the asynchronicity is reduced in the *exo* approach and the transition structure, TS1 *exo* becomes almost synchronous (WBI, C–C=0.36, C–O=0.35).

In the reaction of benzaldehyde with isoprene, the transition structures resulting from the *para* approach of the diene (O/Me, 1:4) are comparatively more asynchronous (WBI, C–C=ca. 0.46, C–O=0.33) than the transition structures obtained from the *meta* approach (O/Me, 1:3) (WBI, C–C=ca. 0.45, C–O=ca. 0.36).

The HDA reactions of benzaldehyde in the presence of ethylaluminium dichloride and boron trifluoride as catalysts are also

#### Table 1

Computed reactions of aromatic aldehydes with 1,3-diene in the absence of the catalyst and in the presence of a catalyst (Scheme 1)

Reac. no.	Z	$R^1 R^2 R^3$	Approach of the diene	TS	Relative energy (kcal $mol^{-1}$ )	
					$\Delta H^{\neq}$	$\Delta H^{\circ}$
1	Nil	H Me Me	endo	TS1 (endo)	29.72 (30.47)	-9.71 (-8.45)
2	Nil	H Me Me	ехо	TS1 (exo)	30.19 (30.89)	-12.53 (-11.21)
3	Nil	Cl Me Me	endo	TS2	28.88 (29.39)	-10.29 (-9.18)
4	Nil	H H Me	endo (O/Me, para)	TS3	29.33 (30.10)	-9.14 (-7.82)
5	Nil	H Me H	endo (O/Me, meta)	TS4	31.30 (32.15)	-9.19 (-7.86)
6	Nil	Cl H Me	endo (O/Me, para)	TS5	28.54 (29.12)	-9.71 (-8.59)
7	Nil	Cl Me H	endo (O/Me, meta)	TS6	30.59 (31.23)	-9.83 (-8.70)
8	BF <sub>3</sub>	H Me Me	endo	TS7	14.59 (14.24)	-12.29 (-9.48)
9	EtAlCl <sub>2</sub>	H Me Me	endo	TS8	14.34 (14.71)	-4.63 (-2.67)
10	TiCl <sub>4</sub>	H Me Me	endo	TS9	17.44 (15.29)	-2.50(-0.54)
11	TiCl <sub>4</sub>	Cl Me Me	endo	TS10	17.05 (14.84)	-3.39 (-1.56)
12	TiCl <sub>4</sub>	H H Me	endo (O/Me, para)	TS11	17.62 (15.41)	-4.76 (-2.62)
13	TiCl <sub>4</sub>	H Me H	endo (O/Me, meta)	TS12	23.24 (21.31)	-4.72 (-2.53)
14	TiCl <sub>4</sub>	Cl H Me	endo (O/Me, para)	TS13	17.27 (14.92)	-5.41 (-3.48)
15	TiCl <sub>4</sub>	Cl H H	endo (O/Me, meta)	TS14	22.59 (20.39)	-5.45 (-3.49)

Relative energy values for the solvent phase (toluene) are given in parentheses.

The HDA reactions of benzaldehyde with DMB have been computed involving the *endo* as well as the *exo* approaches of the diene. As reported in other HDA reactions of the aldehydes,<sup>12,13</sup> the *endo* approach in the present case also has preference over the *exo* approach by ca. 0.5 kcal mol<sup>-1</sup>. found to involve concerted, but asynchronous transition structures (Fig. 2). Earlier attempts<sup>10a</sup> to locate a concerted transition state in the HDA reaction of benzaldehyde with Danishefsky's diene in the presence of  $(MeO)_2$ AlMe as catalyst failed. The asynchronicity in these cases increases further and these reactions in fact lie on the



**Fig. 1.** B3LYP/6-31G(d,p) optimized geometries of the transition structures in the uncatalyzed HDA reactions along with the bond distances (in Å) and Wiberg bond index (WBI) in parentheses.



Fig. 2. B3LYP/6-31G(d,p) optimized geometries of the transition structures in the HDA reactions catalyzed by BF<sub>3</sub> and by EtAlCl<sub>2</sub> along with the bond distances (in Å) and Wiberg bond index in parentheses.

border-line between two distinct types of mechanisms, namely the pericyclic mechanism and the stepwise ionic mechanism. The latter type of mechanism is found to operate in the presence of TiCl<sub>4</sub> as catalyst, discussed later.

The HDA reaction of benzaldehydes with DMB in the presence of Ti(IV) chloride occurs in two steps, the first step leading to the zwitterionic intermediate being rate determining. The optimized geometries of the first and the second transition structures (TS9i and TS9ii, respectively) along with that of the intermediate involved in the HDA reaction of benzaldehyde with DMB in the presence of TiCl<sub>4</sub> are shown (Fig. 3).



**Fig. 3.** B3LYP/6-31G(d,p) optimized geometries of the first and the second transition structures (**TS9i** and **TS9ii**, respectively) and the zwitterionic intermediate (**Int9**) involved in the HDA reaction of benzaldehyde with 2,3-dimethyl-1,3-butadiene catalyzed by TiCl<sub>4</sub>.

It may be noted that formation of the C–C bond in the first transition structure, TS9i is quite advanced (occupancy, 1.70e; bond distance, 1.855 Å; WBI, 0.59) and approaches the reaction intermediate, Int9. The second transition state, TS9ii is not much different from the intermediate, i.e., it is reached quite early. The LUMOs of benzaldehyde (1) and of its complexes with BF<sub>3</sub> (2), EtAlCl<sub>2</sub> (3), and TiCl<sub>4</sub> (4) and the HOMOs of DMB (5) and isoprene (6) are shown (Fig. 4).

It is noteworthy that polarization of the LUMO centered on the carbonyl group of benzaldehyde is not much altered on its complexation with BF<sub>3</sub> and EtAlCl<sub>2</sub>, although their energies are lowered. It explains the involvement of a concerted transition state in all the three cases, and the reaction becoming faster in the presence of BF<sub>3</sub> or EtAlCl<sub>2</sub>. However, on complexation with TiCl<sub>4</sub>, polarization of the LUMO on the carbonyl group changes remarkably, the lobe on the carbonyl oxygen merging with the d orbital of the titanium atom due to  $d\pi \rightarrow p\pi$  bonding. Due to this reason, carbonyl carbon becomes significantly positively charged, thus inducing a stepwise ionic mechanism.

2.1.2. Energetics. Thermodynamic data of the calculated model HDA reactions are given in the Supplementary data TS2. All the reactions are exothermic, but as expected, the entropy of the reaction decreases substantially. Thus it is the activation enthalpy  $(\Delta H^{\neq})$ , which plays the main role in the occurrence of the reaction.

The activation enthalpy of the uncatalyzed HDA reaction of benzaldehyde with DMB in the gas phase ( $\Delta H^{\neq}$ =29.72 kcal mol<sup>-1</sup>)



**Fig. 4.** LUMOs of benzaldehyde (1) and its complexes with  $BF_3$  (2),  $EtAlCl_2$  (3), and  $TiCl_4$  (4) and the HOMOs of DMB (5) and isoprene (6) along with their energies.

is quite high, which increases further by ca. 1 kcal mol<sup>-1</sup> in toluene. The presence of an electron-withdrawing group (EWG) like chlorine in the phenyl ring is also not much effective, as it brings down  $\Delta H^{\neq}$  only marginally, just by ca. 1 kcal mol<sup>-1</sup> in the gas phase or in solution. It explains the inertness of aromatic aldehydes towards HDA reaction under uncatalyzed conditions.

The presence of BF<sub>3</sub> or EtAlCl<sub>2</sub> as catalyst brings down the  $\Delta H^{\neq}$ in the gas phase substantially (ca. 15 kcal mol<sup>-1</sup>), which is further reduced marginally in toluene. It indicates that the HDA reaction of aromatic aldehydes with DMB should be possible in the presence of any of these catalysts. As described later, the HDA reaction of mnitrobenzaldehyde with DMB could be accomplished successfully in the presence of EtAlCl<sub>2</sub>. The use of TiCl<sub>4</sub> as catalyst not only lowers the  $\Delta H^{\neq}$  by ca. 12 kcal mol<sup>-1</sup> in the gas phase, which is further reduced in the solvent by 2 kcal mol<sup>-1</sup>, it also changes the mechanism of the reaction from pericyclic to the stepwise ionic. Now the reaction occurs in two steps, the first step being rate determining. Although it has been possible to locate the second transition state, it is very similar to the intermediate and is only 0.11 kcal mol<sup>-1</sup> higher in energy than the intermediate in the gas phase (0.46 kcal  $mol^{-1}$  in the solvent). The presence of chlorine atom in the phenyl ring is not of much consequence and there is no significant change in the  $\Delta H^{\neq}$  value for the TiCl<sub>4</sub> catalyzed reaction. As regards the regioselectivity of the reaction with isoprene in the presence of TiCl<sub>4</sub> catalyst, the path leading to the para regioisomer (O/Me, 1:4) has  $\Delta H^{\neq}$  lower than the path giving *meta* regioisomer (O/Me, 1:3) by ca. 6 kcal mol<sup>-1</sup>. The activation enthalpies of the HDA reactions under different conditions are depicted graphically (Fig. 5).

It may be inferred from the above theoretical results that the HDA reactions of benzaldehydes with simple dienes, such as DMB or isoprene should be possible only in the presence of a Lewis acid



**Fig. 5.** Relative activation enthalpies for the reaction of benzaldehyde with 2,3dimethyl-1,3-butadiene without catalyst and in the presence of various catalysts.

as catalyst. Encouraged by these results, we investigated the HDA reactions of four aromatic aldehydes  $(1_{a-d})$  with DMB and isoprene.

#### 2.2. Experimental results

Aromatic aldehydes (**1**) on reacting with 1,3-diene (**2**) in the presence of a catalyst in toluene at room temperature afford 3,6-dihydro-2*H*-pyran derivatives (**3**) (Scheme 2).

The reaction is complete in ca. 1-2 h at room temperature. The presence of EWG (Table 2, entries 1, 2, 5, 6, 7) makes the reaction



Scheme 2. HDA reaction of aromatic aldehyde with 1,3-diene in the presence of catalyst.

 Table 2

 The HDA reactions of aromatic aldehydes in the presence of a catalyst

Entry	$\mathbb{R}^1$	R <sup>2</sup>	Catalyst (mol %)	Yield (%)	Time (h)
1	4-Cl	Me	TiCl <sub>4</sub> (15)	74	1.50
2	3-NO2	Me	TiCl <sub>4</sub> (15)	84	1.25
3	2-OMe	Me	TiCl <sub>4</sub> (15)	56	2.50
4	2,5-(OMe) <sub>2</sub>	Me	TiCl <sub>4</sub> (15)	52	2.00
5	3-NO <sub>2</sub>	Me	EtAlCl <sub>2</sub> (15)	79	1.00
6	4-Cl	Н	TiCl <sub>4</sub> (15)	70	1.75
7	3-NO <sub>2</sub>	Н	TiCl <sub>4</sub> (15)	72	1.50

faster. As described earlier, the relative activation energy barrier for the HDA reaction in the presence of  $EtAlCl_2$  is smaller than in the presence of  $TiCl_4$ ; it is supported by the experimental results, as the HDA reaction of  $1_b$  with DMB in the presence of  $EtAlCl_2$ (Table 2, entry 5) is complete sooner than in the presence of  $TiCl_4$ (Table 2, entry 2). All the reactions occur with complete stereoselectivity, only one product (in fact a racemic mixture of two enantiomers) being formed in the reaction with DMB. As regards the regioselectivity, experimental results are in complete agreement with the theoretical results; the reaction of *p*-chlorobenzaldehyde (1b) with isoprene in the presence of  $TiCl_4$ (15 mol %) gives only the regioisomer having O/Me in the 1:4positions.

On using less than 15 mol % of the catalyst, unreacted aldehyde is detected (TLC). Furthermore, if the reaction mixture is not quenched just after completion, aldehyde is regenerated. Similar observations have been made earlier.<sup>16,17</sup>

All the products are pale yellow to orangish-yellow syrupy mass, which have been characterized on the basis of IR spectra. <sup>1</sup>H and <sup>13</sup>C NMR spectra and elemental analysis. In the IR spectra, an intense absorption band in the region  $\nu$  1099–1090 cm<sup>-1</sup> results due to C–O stretching vibrations. In the <sup>1</sup>H NMR spectra, protons  $H_B$  and  $H_C$  (at C3) are diastereotopic and they constitute an ABC spin system with the proton  $H_A$  (at C2): proton  $H_A$  gives a double doublet (dd) at  $\delta$  4.49–4.91 ppm ( $^3\!J_{\rm HA,HB}{=}9.0{-}10.5$  Hz,  ${}^{3}J_{\text{HA,HC}}$ =3.6–6.0 Hz), H<sub>B</sub> a dd at  $\delta$  2.11–2.91 ppm ( ${}^{2}J_{\text{HB,HC}}$ =14.1–16.8 Hz,  ${}^{3}J_{\text{HA,HB}}$ =9.0–10.5 Hz) and H<sub>C</sub> a dd at δ 2.11–3.06 ppm (<sup>2</sup>*J*<sub>HB,HC</sub>=14.1–16.8 Hz, <sup>3</sup>*J*<sub>HA,HC</sub>=3.6–6.0 Hz). Likewise, protons H<sub>D</sub> and H<sub>E</sub> at C6 are diastereotopic forming an AB spin system and each gives a doublet at  $\delta$  4.18–4.35 ppm  $({}^{2}J_{\text{HD,HE}}=9.0-9.9 \text{ Hz})$  and at  $\delta 4.05-4.35 \text{ ppm} ({}^{2}J_{\text{HD,HE}}=9.0-9.9 \text{ Hz})$ , respectively. The methyl groups at C4 and C5 give singlets in the region  $\delta$  1.57–1.79 ppm. Other protons absorb in the expected regions. In the <sup>13</sup>C NMR spectrum, the carbon atoms C2 and C6 absorb typically at  $\delta$  70.6–75.4 and  $\delta$  66.4–70.1 ppm, respectively. The other carbon atoms give signals in the expected regions.

#### 3. Conclusion

We have demonstrated theoretically that the HDA reactions of the aromatic aldehydes with simple dienes, such as DMB or isoprene can be catalyzed by Lewis acid, namely BF<sub>3</sub>, EtAlCl<sub>2</sub> or TiCl<sub>4</sub>. In the case of the first two catalysts, the reaction follows a concerted mechanism with the asynchronous transition states, but TiCl<sub>4</sub> catalyzed reaction occurs through a stepwise ionic mechanism involving a zwitterionic intermediate. The reaction with isoprene is expected to take place with complete regioselectivity to give the regioisomer having O/Me in the 1:4 positions. These results have been verified experimentally, when HDA reactions of aromatic aldehydes with DMB and with isoprene have been accomplished successfully in the presence of 15 mol % TiCl<sub>4</sub> to give 3,6-dihydro-2*H*-pyran derivatives in high yields. That EtAlCl<sub>2</sub> can be used as catalyst in place of TiCl<sub>4</sub>, has been demonstrated for the HDA reaction of *m*-nitrobenzaldehyde with DMB.

#### 4. Computational methods

In a number of investigations of the DA and HDA reactions, the activation barriers calculated at the DFT level using the B3LYP hybrid functional<sup>18,19</sup> have been found in good agreement with the experimental results. In the present study therefore all geometries of the reactants, cycloadducts, and the corresponding transition structures were optimized in the gas phase at the B3LYP/ 6–31G(d,p) level of theory using Gaussian 03 suite of program,<sup>20</sup> generating basis sets for Ti at the 6-31G(d,p) level.

Frequency calculations were done at the same level to determine zero-point correction energies and to characterize the transition structure by the presence of one and only one imaginary frequency corresponding to the movement of the atoms in the direction of the bond formation. The intrinsic reaction coordinate (IRC)<sup>21,22</sup> calculations starting at the respective transition structure were carried out at the B3LYP/6-31G(d,p) level to confirm its connection with the corresponding reactants and the cycloadducts. The natural bond orbital (NBO) analysis<sup>23</sup> was employed for the evaluation of the forming bonds. Following the reports of the other research groups<sup>24–27</sup> on the use of the self-consistent reaction field polarizable continuum model (SCRF-PCM)<sup>28,29</sup> for studying the solvent effect, we also used this model and calculated single point energy of the B3LYP/6-31G(d,p) gas phase optimized stationary points at the same level using SCRF method based on Tomasi's polarizable continuum model (PCM).<sup>30</sup> FMOs were generated by using Chemcraft software.<sup>31</sup>

#### 5. Experimental section

Commercially available aldehydes, DMB, and isoprene were used without further purification. TiCl<sub>4</sub> (1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>) and EtAlCl<sub>2</sub> (1.8 M solution in toluene) were purchased from Sigma–Aldrich. Solvents were freshly dried and distilled.

IR spectra were recorded on NaCl plate on Perkin Elmer Precisely FT-IR spectrometer. NMR spectra were recorded on Bruker-DPX-300 MHz spectrometer: <sup>1</sup>H NMR at a frequency of 300.13 MHz and <sup>13</sup>C NMR at a frequency of 75.48 MHz using TMS as the internal reference. The C, H, N elemental analyses were done on FLASH Ea 1112 series CHN analyzer at the School of Chemistry, University of Hyderabad, Hyderabad, India.

## 5.1. General procedure for the TiCl<sub>4</sub> and EtAlCl<sub>2</sub> catalyzed HDA reaction (3b,o-s)

Aldehyde 1 (3 mmol) was dissolved in toluene (20 mL) taken in a 100 mL R.B. flask at room temperature (  $\sim$  25 °C). To this solution was added the solution of TiCl<sub>4</sub> (0.45 mmol, 0.45 mL 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) or EtAlCl<sub>2</sub> (0.45 mmol, 0.25 mL 1.8 M solution in toluene) when vellow to orangish brown color developed. After stirring the resulting turbid solution at room temperature for about 30 min, two-fold excess of the diene 2 (6 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1-2.5 h, progress of the reaction being monitored by TLC (solvent: pet. ether 60-80 °C/EtOAc: 80:20 v/v %). After completion of the reaction, the reaction mixture was quenched with water (10 mL) and the organic layer was separated. The aqueous layer was extracted with toluene  $(2 \times 2 \text{ mL})$ . The combined extracts were dried over anhydrous sodium sulfate and the solution was concentrated to ca. 2–3 mL. The crude product was purified by column chromatography over silica gel (eluent; pet. ether 60-80 °C/EtOAc: 98:2 v/v%). A viscous oil 3 was obtained.

5.1.1. 3,6-Dihydro-4,5-dimethyl-2-(4'-chlorophenyl)-2H-pyran **3b**. From 4-chlorobenzaldehyde (421 mg, 3 mmol) and DMB (493 mg, 6 mmol, 0.68 mL) **3b** (490 mg, 74%) was obtained as a colorless viscous oil; [found: C, 70.25; H, 6.85.  $C_{13}H_{15}OCI$  requires C, 70.11; H, 6.79%];  $R_f$  (25% EtOAc/pet. ether) 0.59;  $\nu_{max}$  (NaCl plate) 2956, 2922, 2868, 1491, 1449, 1405, 1382, 1090, 1014, 821 cm<sup>-1</sup>;  $\delta_{H}$  (CDCl<sub>3</sub>, 25 °C) 7.78 (d,  ${}^{3}J_{HH}$ =6.6 Hz, 2H, H2′, H6′), 7.47 (d,  ${}^{3}J_{HH}$ =6.6 Hz, 2H, H3′, H5′), 4.49 (dd,  ${}^{3}J_{HAHB}$ =10.5 Hz,  ${}^{3}J_{HAHC}$ =3.9 Hz, 1H, 2-H<sub>A</sub>), 4.18 (d,  ${}^{2}J_{HDHE}$ =15.6 Hz, 1H, 6-H<sub>D</sub>), 4.08 (d,  ${}^{2}J_{HDHE}$ =15.6 Hz, 1H, 6-H<sub>E</sub>), 2.26–2.17 (m, 2H, 3-H<sub>B</sub>, 3-H<sub>C</sub>), 1.67 (s, 3H, 5-Me), 1.57 ppm (s, 3H, 4-Me);  $\delta_{C}$  (CDCl<sub>3</sub>, 25 °C): 141.2, 132.9, 128.0, 126.9, 124.5, 123.5, 75.4 (2-C), 70.7 (6-C), 38.5 (3-C), 18.8, 13.8 ppm.

5.1.2. 3,6-*Dihydro*-4,5-*dimethyl*-2-(3'-*nitrophenyl*)-2*H*-*pyran* **30**. From 3-nitrobenzaldehyde (453 mg, 3 mmol) and DMB (493 mg, 6 mmol, 0.68 mL) **30** (590 mg, 84%) was obtained as a yellow viscous oil; [found: C, 66.85; H, 6.54; N, 6.12. C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 66.94; H, 6.48; N, 6.00%]; *R*<sub>f</sub> (10% EtOAc/pet. ether) 0.67;  $\nu_{max}$  (NaCl plate) 2958, 2868, 1531, 1454, 1350, 1099, 805 cm<sup>-1</sup>;  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 25 °C)=8.26 (d, <sup>4</sup>*J*<sub>HH</sub>=1.8 Hz, 1H, H2'), 8.21 (dd, <sup>3</sup>*J*<sub>HH</sub>=8.1 Hz, <sup>4</sup>*J*<sub>HH</sub>=1.8 Hz, 1H, H4'), 7.72 (d, <sup>3</sup>*J*<sub>HH</sub>=7.8 Hz, 1H, H6'), 7.52 (t, <sup>3</sup>*J*<sub>HH</sub>=7.8 Hz, <sup>3</sup>*J*<sub>HH</sub>=8.1 Hz, 1H, H5'), 4.65 (dd, <sup>3</sup>*J*<sub>HAHB</sub>=9.9 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=6.0 Hz, 1H, 2-H<sub>A</sub>), 4.23 (d, <sup>2</sup>*J*<sub>HDHE</sub>=15.6 Hz, 1H, 6-H<sub>D</sub>), 4.18 (d, <sup>2</sup>*J*<sub>HDHE</sub>=15.6 Hz, 1H, 6-H<sub>E</sub>), 3.06 (dd, <sup>2</sup>*J*<sub>HBHC</sub>=15.6 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=6.0 Hz, 1H, 3-H<sub>C</sub>), 2.63 (dd, <sup>2</sup>*J*<sub>HBHC</sub>=15.6 Hz, <sup>3</sup>*J*<sub>HAHB</sub>=9.9 Hz, 1H, 3-H<sub>C</sub>), 1.60 ppm (s, 3H, 4-Me);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 25 °C) 148.3, 144.9, 132.0, 129.3, 124.7, 123.2, 122.4, 121.0, 75.0 (2-C), 70.2 (6-C), 38.3 (3-C), 18.3, 13.9 ppm.

5.1.3. 3,6-*D*ihydro-4,5-*d*imethyl-2-(2'-methoxyphenyl)-2H-pyran **3p**. From 2-methoxybenzaldehyde (408 mg, 3 mmol) and DMB (493 mg, 6 mmol, 0.68 mL) **3p** (370 mg, 56%) was obtained as an orange viscous oil. [found: C, 77.19; H 8.42 requires C, 77.03; H, 8.31]; *R*<sub>f</sub> (15% EtOAc/pet. ether) 0.80; *v*<sub>max</sub> (NaCl plate) 2923, 2837, 1588, 1493, 1463, 1438, 1244, 1099, 1050, 1029, 753 cm<sup>-1</sup>;  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 25 °C) 7.47 (d, <sup>4</sup>*J*<sub>HH</sub>=7.5 Hz, 1H, 6'-H), 7.26 (t, <sup>3</sup>*J*<sub>HH</sub>=8.1 Hz, <sup>3</sup>*J*<sub>HH</sub>=7.5 Hz, 1H, H4'), 6.98 (t, <sup>3</sup>*J*<sub>HH</sub>=7.5 Hz, 1H, H5'), 6.85 (d, <sup>3</sup>*J*<sub>HH</sub>=8.1 Hz, 1H, H3'), 4.91 (dd, <sup>3</sup>*J*<sub>HAHB</sub>=9.0 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=5.1 Hz, 1H, 2-H<sub>A</sub>), 4.18 (d, <sup>2</sup>*J*<sub>HDHE</sub>=11.1 Hz, 1H, 6-H<sub>D</sub>), 4.05 (d, <sup>2</sup>*J*<sub>HDHE</sub>=11.1 Hz, 1H, 6-H<sub>E</sub>), 3.82 (s, 3H, 2'-OMe), 2.91 (dd, <sup>2</sup>*J*<sub>HBHC</sub>=14.7 Hz, <sup>3</sup>*J*<sub>HAHE</sub>=9.0 Hz, 1H, 3-H<sub>D</sub>), 1.67 (s, 3H, 5-Me), 1.58 ppm (s, 3H, 4-Me);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 25 °C) 155.8, 129.3, 128.0, 124.3, 120.8, 110.6, 110.2, 70.6 (2-C), 70.2 (6-C), 55.5 (2'-OMe), 37.4 (3-C), 17.2, 15.0 ppm.

5.1.4. 3,6-Dihydro-4,5-dimethyl-2-(2',5'-dimethoxyphenyl)-2H-pyran **3q**. From 2,5-dimethoxybenzaldehyde (500 mg, 3 mmol) and DMB (493 mg, 6 mmol, 0.68 mL) **3q** (390 mg, 52%) was obtained as an orange brown viscous oil. [found: C, 72.72; H, 8.21. C<sub>15</sub>H<sub>20</sub>O<sub>3</sub> requires C, 72.55; H, 8.13]; *R*<sub>f</sub> (12.5% EtOAc/pet. ether) 0.68; *v*<sub>max</sub> (NaCl plate) 2951, 2927, 2856, 1500, 1444, 1380, 1260, 1217, 1097, 1049, 799 cm<sup>-1</sup>;  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 25 °C) 7.08 (s, 1H, H6'), 6.79 (d, <sup>3</sup>*J*<sub>HH</sub>=6.3 Hz, 1H, H3'), 6.75 (d, <sup>3</sup>*J*<sub>HH</sub>=6.3 Hz, 1H, H4'), 4.88 (dd, <sup>3</sup>*J*<sub>HAHB</sub>=9.6 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=4.5 Hz, 1H, 2-H<sub>A</sub>), 4.21 (d, <sup>2</sup>*J*<sub>HDHE</sub>=9.9 Hz, 1H, 6-H<sub>D</sub>), 4.07 (d, <sup>2</sup>*J*<sub>HDHE</sub>=9.9 Hz, 1H, 6-H<sub>E</sub>), 3.80 (s, 6H, 2'-OMe, 5'-OMe), 2.88 (dd, <sup>2</sup>*J*<sub>HBHC</sub>=14.1 Hz, <sup>3</sup>*J*<sub>HAHB</sub>=9.6 Hz, 1H, 3-H<sub>B</sub>), 2.73 (dd, <sup>2</sup>*J*<sub>HBHC</sub>=14.1 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=4.5 Hz, 1H, 3-H<sub>C</sub>), 1.67 (s, 3H, 5-Me), 1.59 ppm (s, 3H, 4-Me);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 25 °C) 153.9, 150.0, 132.2, 124.3, 113.9, 113.0, 111.4, 70.9 (2-C), 70.4 (6-C), 55.3 (2'-OMe, 5'-OMe), 37.3 (3-C), 18.3, 13.9 ppm.

5.1.5. 3,6-Dihydro-4-methyl-2-(4'-chlorophenyl)-2H-pyran **3r**. From 4-chlorobenzaldehyde (421 mg, 3 mmol) and isoprene (408 mg, 6 mmol, 0.60 mL) **3r** (436 mg, 70%) was obtained as a yellow viscous oil. [Found: C, 69.23; H, 6.41. C<sub>12</sub>H<sub>13</sub>OCl requires C, 69.07; H, 6.28];  $R_f$  (25% EtOAc/pet. ether) 0.78;  $\nu_{max}$  (NaCl plate) 2964, 2907, 1594, 1491, 1412, 1265, 1091, 1014, 820 cm<sup>-1</sup>;  $\delta_{H}$  (CDCl<sub>3</sub>, 25 °C) 8.01 (d,  ${}^{3}J_{HH}$ =8.4 Hz, 2H, H2', H6'), 7.83 (d,  ${}^{3}J_{HH}$ =8.4 Hz, 2H, H3', H5'),

5.50 (s, 1H, 5-H), 4.51 (dd, <sup>3</sup>*J*<sub>HAHB</sub>=10.5 Hz, <sup>3</sup>*J*<sub>HAHC</sub>=3.6 Hz, 1H, 2-H<sub>A</sub>), 4.31 (s, 2H, 6-H<sub>D</sub>, 6-H<sub>E</sub>), 2.32–2.12 (m, 2H, 3-H<sub>B</sub>, 3-H<sub>C</sub>), 1.79 ppm (s, 3H, 4-Me).

5.1.6. 3,6-Dihydro-4-methyl-2-(3'-nitrophenyl)-2H-pyran **3s**. From 3-nitrobenzaldehyde (453 mg, 3 mmol) and isoprene (408 mg, 6 mmol, 0.60 mL) **3s** (475 mg, 72%) was obtained as a yellow viscous oil. [Found: C, 65.86; H, 5.91; N, 6.28.  $C_{12}H_{13}NO_3$  requires C, 65.74; H, 5.98; N 6.39];  $R_f$  (10% EtOAc/pet. ether) 0.67;  $\nu_{max}$  (NaCl plate) 2929, 1531, 1481, 1446, 1348, 1122, 1095, 1044, 813 cm<sup>-1</sup>;  $\delta_{H}$  (CDCl<sub>3</sub>, 25 °C) 8.27 (d, <sup>4</sup>J<sub>HH</sub>=1.5 Hz, 1H, H2'), 8.14 (dd, <sup>3</sup>J<sub>HH</sub>=8.1 Hz, <sup>4</sup>J<sub>HH</sub>=1.5 Hz, 1H, H4'), 7.73 (d, <sup>3</sup>J<sub>HH</sub>=7.8 Hz, 1H, H6'), 7.52 (t, <sup>3</sup>J<sub>HH</sub>=7.8 Hz, <sup>3</sup>J<sub>HH</sub>=8.1 Hz, 1H, H5'), 5.53 (s, 1H, H5), 4.64 (dd, <sup>3</sup>J<sub>HAHB</sub>=9.6 Hz, <sup>3</sup>J<sub>HAHC</sub>=4.2 Hz, 1H, 2-H<sub>A</sub>), 4.35 (d, <sup>2</sup>J=2.1 Hz, 2H, 6-H<sub>D</sub>, 6-H<sub>E</sub>), 2.28 (dd, <sup>2</sup>J<sub>HBHC</sub>=16.8 Hz, <sup>3</sup>J<sub>HAHB</sub>=9.6 Hz, 1H, 3-H<sub>B</sub>), 2.18 (dd, <sup>2</sup>J<sub>HBHC</sub>=16.8 Hz, <sup>3</sup>J<sub>HAHC</sub>=4.2 Hz, 1H, 3-H<sub>C</sub>), 1.77 ppm (s, 3H, 4-Me);  $\delta_{C}$  (CDCl<sub>3</sub>, 25 °C) 148.3, 144.9, 131.9, 131.4, 129.3, 122.3, 120.9, 119.9, 74.5 (2-C), 66.4 (6-C), 37.5 (3-C), 22.9 (5-Me) ppm.

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#### Supplementary data

Total energies of reactants, transition structures, intermediates and cycloadducts in gas phase and in toluene (Table S1), standard and activation enthalpies, entropies and Gibbs free energies of the computed reactions, 1–15 at the B3LYP/6-31G(d,p)level (Table S2) and Cartesian coordinates of the geometries optimized at B3LYP/6-31G\*\* (generated basis sets) level (Table S3). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/ j.tet.2013.11.077.

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