



## Theory-guided design of Brønsted acid-assisted phosphine catalysis: synthesis of dihydropyrones from aldehydes and allenates

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### ABSTRACT

The phosphine-catalyzed addition of 2,3-butadienoates to aldehydes has been extended to the formation of disubstituted dihydro-2-pyrones. The requisite shift in equilibrium of the intermediate zwitterionic  $\beta$ -phosphonium dienolates toward the *s-cis* intermediate was accomplished through the use of a Brønsted acid additive, which disrupts the favorable Coulombic interaction present in the *s-trans* intermediate. The detailed nature of the synergistic interactions involving the Brønsted acid additives and phosphine involved in the formation of *s-cis*  $\beta$ -phosphonium dienolates was analyzed through a series of DFT calculations. Unlike previously reported annulations of aldehydes with allenates, where trialkylphosphines are optimal catalysts, in this study triphenylphosphine was also found for the first time to be a suitable catalyst for the synthesis of dihydropyrones. This method provides a one-step route toward functionalized dihydropyrones from simple, stable starting materials. In addition, new reaction pathways of phosphine-catalyzed allene annulations are unveiled, with the formation of dihydropyrones being the first example of dual activation in this sphere.

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### 1. Introduction

Dual activation is a powerful technology in the development of novel reaction pathways.<sup>1</sup> In particular, the combined use of compatible acidic and basic reagents to activate multiple reactive centers in reactants can have a powerful synergistic effect on rate and reaction modality; additionally, enantioselective processes are possible with a single chiral activator.<sup>2</sup> We became interested in applying this concept of dual activation to the phosphine-catalyzed annulations of 2,3-butadienoates. Although numerous catalytic asymmetric Morita–Baylis–Hillman (MBH) processes have been reported employing chiral Brønsted acids that are compatible with nucleophilic Lewis bases,<sup>3,4</sup> the literature examples of dual activation for the mechanistically similar nucleophilic phosphine-catalyzed allene annulations are rare.<sup>5</sup> Indeed, the use of an additive to manipulate the reactivity in phosphine-catalyzed annulations of allenes has as of yet been explored only for the synthesis of dihydropyrones, as we describe in further detail below.

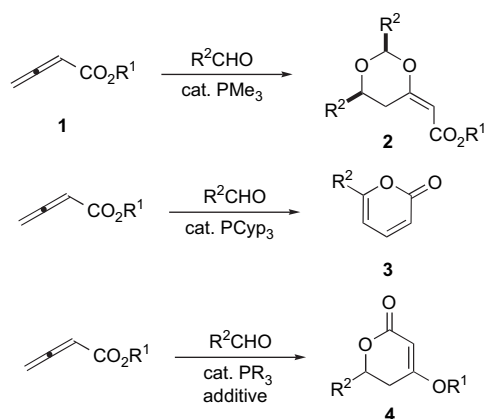
There is much evidence supporting dual activation in the nucleophile-catalyzed MBH reaction.<sup>3</sup> In addition to using a Lewis basic nucleophile as a catalyst, the presence of certain hydrogen bond donors<sup>4</sup> can dramatically increase the rate of reaction, due in

part to the increase in concentration of the zwitterionic intermediate.<sup>6</sup> The addition of an alcohol or water has also been demonstrated in several cases to substantially increase the reaction rate,<sup>7</sup> which is often attributed to added assistance during the proton transfer steps.<sup>8</sup> Chiral Lewis and Brønsted-acidic components possessing free hydrogen bond donors have been applied to activate the electrophilic partner, thereby increasing the reaction rate and inducing facial selectivity.<sup>9</sup> Bifunctional catalysis,<sup>10</sup> a particularly promising type of dual activation, has also led to many extremely rewarding discoveries in the MBH reaction. Such catalysts, which commonly comprise a nucleophilic reactive site and a hydrogen bond donor to activate the electrophilic partner,<sup>11</sup> increase the rate of the reaction and its scope, frequently inducing high levels of enantiomeric excess in the products. The power of dual activation by means of nucleophilic catalysis in conjunction with an additional component is well documented.<sup>1,2</sup>

The scope of phosphine-catalyzed annulations of 2,3-butadienoates with unsaturated electrophiles has been greatly expanded over the last decade or so.<sup>12</sup> In addition to the reported reactions of electron-poor alkenes and imines, we have previously demonstrated that aldehydes are viable electrophiles for the selective formation of dioxane and pyrone oxacycles (Scheme 1).<sup>13</sup> The use of small phosphines, such as trimethylphosphine, leads to the formation of dioxane products (**2**) whereas bulky phosphines form pyrone products (**3**) exclusively. It is believed that the key mechanistic difference lies in the equilibrium between the two isomeric

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**Scheme 1.** Phosphine-catalyzed annulations of 2,3-butadienoates with aldehydes as electrophiles.

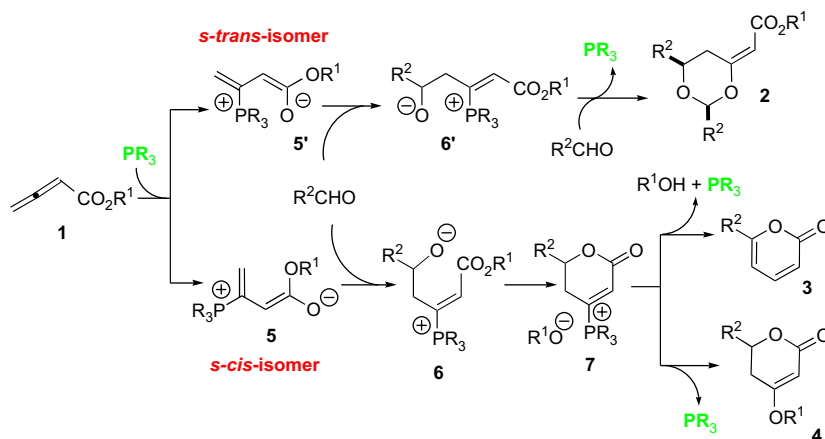
$\beta$ -phosphonium dienolates formed upon addition of the tertiary phosphine catalyst to the butadienoate; we suspected that an alternative means of influencing this equilibrium, other than changing the phosphine's size, would enable the formation of dihydropyrene oxacycles (**4**).

## 2. Results and discussion

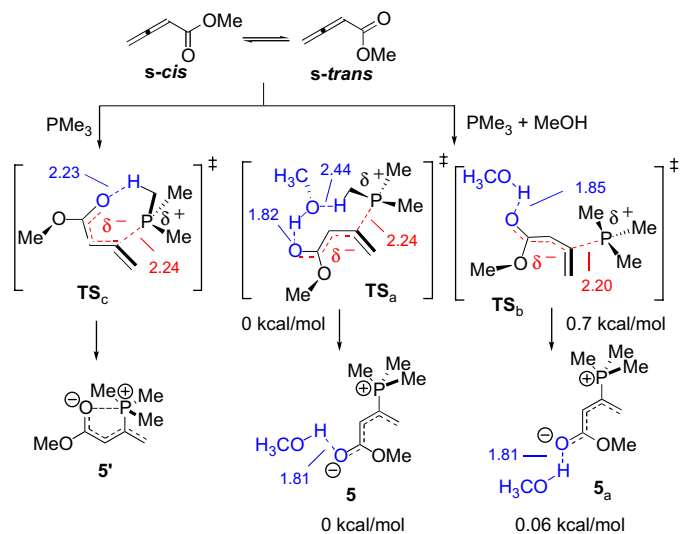
In the first step of the nucleophilic phosphine catalysis of allenes, the addition of the phosphine catalyst to the 2,3-butadienoate **1** results in an equilibrium mixture of dienolates **5** and **5'** (Scheme 2).<sup>13c</sup> If the phosphine is small, such as trimethylphosphine, then the intermediate dienolate **5'** having *s-trans* geometry is dominant because of Coulombic attraction between the phosphonium unit and the delocalized negative charge of the enolate alkoxide moiety. The addition of an aldehyde to the *s-trans* intermediate results in the formation of the  $\beta$ -phosphonium enoate **6'** having *Z* geometry, which incorporates a second equivalent of aldehyde and undergoes 6-*exo-trig* cyclization onto the enoate to release the catalyst and form the dioxane **2**.<sup>13a</sup> In an alternative reaction pathway, if the phosphine catalyst is bulky, for instance triisopropyl-, tricyclohexyl-, or tricyclopentylphosphine, steric hindrance around the phosphine unit appears to disrupt the favorable Coulombic interaction and shift the equilibrium toward the dienolate **5** having *s-cis* geometry. Upon addition of the aldehyde to the  $\gamma$ -carbon atom,<sup>13b</sup> the  $\beta$ -phosphonium enoate **6** having *E* geometry is formed. The spatial proximity between the alkoxide and enoate units in intermediate **6** allows lactonization, resulting in the

formation of **7**. The concomitantly generated alkoxide  $R^1O^-$  facilitates deprotonation of the  $\beta$ -phosphonium lactone **7**; the resulting zwitterion proceeds to form the pyrone **3** and regenerate the phosphine catalyst. We suspect that conjugate addition of the alkoxide followed by facile  $\beta$ -elimination of the phosphine, resulting in dihydropyrene **4**, is blocked by the bulky phosphine required for the formation of **5**. An alternative method for stabilizing the *s-cis*  $\beta$ -phosphonium dienolate **5** would potentially allow a smaller phosphine to act as a catalyst, with subsequent formation of disubstituted dihydropyrenes **4**. Given that the electrostatic attraction between the phosphonium cation and the alkoxide anion facilitates the formation of the *s-trans*  $\beta$ -phosphonium dienolate **5'**, we envisioned the possibility of using hydrogen bond donors to stabilize the alkoxide moiety and induce the desired *s-cis* dienolate **5**. It occurred to us that addition of an alcohol  $R^1OH$  would be especially attractive because the competing reaction pathway to the pyrone **3** would be discouraged.

To evaluate the viability of this mechanistic proposal, we performed a series of quantum chemical calculations rooted within the formalism of the generalized gradient approximation (GGA)-hybrid Kohn–Sham density functional theory (KS-DFT) using Becke's three-parameter exchange functional (B3)<sup>14</sup> with inclusion of Lee, Yang, and Parr's electron correlation method (LYP)<sup>15</sup> and Pople's 6-31G(d) basis set.<sup>16</sup> The reported energies represent computed values from single-point implicit conductor-like polarizable continuum model (CPCM) solvation calculations (benzene  $\epsilon=2.25$ ) performed on B3LYP/6-31G(d)-(CPCM)//B3LYP/6-31G(d)-optimized geometries.<sup>17</sup> All quantum chemical calculations were undertaken using the Gaussian suite of programs G03<sup>18</sup> and Gaussview 3.0.<sup>19</sup> To accomplish this goal, we conducted a systematic survey of the potential energy surface (PES) within the vicinity corresponding to the transition state for  $P^+-C$  bond formation during the phosphine-*to*-allenoate addition in the presence of MeOH (Scheme 3). From this survey, we located two nearly energetically equivalent lowest-energy first-order saddle points **TS<sub>a</sub>** ( $\Delta\Delta G^\ddagger_{\text{solv}}=0$  kcal/mol) and **TS<sub>b</sub>** ( $\Delta\Delta G^\ddagger_{\text{solv}}=0.7$  kcal/mol). The defining metrics of these transition state structures included  $P^+-C$  bond forming distances of 2.24 Å and 2.20 Å, respectively. In addition, present within each structure was a hydrogen bond (H-bond) contact between the MeOH hydroxyl group and the  $O^\delta-$ -carbonyl oxygen atom of the reacting allenoate, measuring 1.82 Å for **TS<sub>a</sub>** and 1.85 Å for **TS<sub>b</sub>**, which functionally impart degrees of stability to these transition states. Upon subsequent optimization of **TS<sub>a</sub>** and **TS<sub>b</sub>** to their respective local minima **5** and **5<sub>a</sub>**, corresponding to the immediate products of  $P^+-C$  bond formation, a most revealing mechanistic feature was unveiled: in the presence of Brønsted-acidic methanol, the intermediate products formed



**Scheme 2.** Formation of dioxanes **2**, 2-pyrones **3**, and dihydro-2-pyrones **4**.



**Scheme 3.** Structures of the transition states and the resulting phosphonium dienolate zwitterions in the presence and absence of methanol.

were the minima **5** and **5<sub>a</sub>** possessing *s-cisoid* geometries. These findings represent a dramatic departure from our previous *in silico* mechanistic studies addressing nucleophilic phosphine-triggered zwitterionic enolate formation in the absence of Brønsted-alcoholic additives (see **5'** in Scheme 3).<sup>20</sup> In our prior studies we established that the *s-trans* enolate **5'** was the direct and most stable product formed from the transition state **TS<sub>c</sub>** of the phosphine-*to*-allenoate addition. Accordingly, based upon our new calculations—in what certainly reflects a cause-and-effect relationship—the addition of a Brønsted acid, in this case methanol, leads to a Boltzmann distribution toward the *s-cis* zwitterions **5** and **5<sub>a</sub>** from favoring the *s-trans* zwitterion **5'** in non-polar media. These two minima, **5** and **5<sub>a</sub>**, vary structurally solely in terms of the relative orientation of their hydrogen-bond-coordinated methanol units.<sup>21</sup>

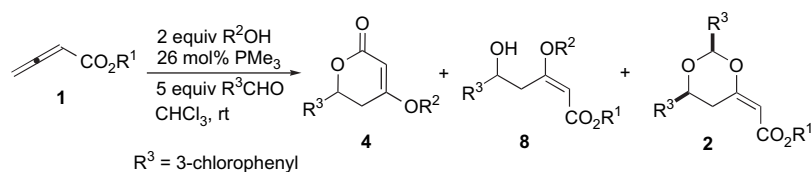
Having verified, through DFT calculations, that addition of a hydrogen bond donor could induce formation of the *s-cis* isomer **5** by disrupting the putative Coulombic attraction stabilizing **5'**, we acted upon this mechanistic insight experimentally. Promisingly, initial experiments using isopropanol and ethanol (Table 1, entries 1 and 2) revealed a small induction of the desired dihydropyrone, but the majority of the product was the dioxane, presumably because the phosphonium dienolate equilibrium favored the undesired *s-trans* isomer **5'**. The use of methanol provided more encouraging results, with an increase in total mass recovery to 78% and the major product being the dihydropyrone (Table 1, entry 3). The second major product was the three-component-coupling adduct **8**, formed from the aldehyde, allenoate, and alcohol, which formed presumably through regeneration of the phosphine catalyst via Michael addition of the alkoxide prior to lactonization of the intermediate **6** (see Scheme 2).<sup>22</sup> We suspected that a decrease in the nucleophilicity of the additive would suppress this interruptive Michael addition. Accordingly, the slightly more-acidic benzyl alcohol provided exclusively the dihydropyrone product **4**, although the mass recovery was unexpectedly low (Table 1, entry 4). This observation led us to explore more-acidic alcohols. We expected that the commercially available halogenated ethanol derivatives, which exhibit decreased nucleophilicity and, simultaneously, decreased *pK<sub>a</sub>* would preferentially induce formation of the desired dihydropyrone (Table 1, entries 5–12). Indeed, a decrease in the yield of the non-cyclic product **8** occurred when we used the less-nucleophilic 2-fluoroethanol and 2-chloroethanol additives (Table 1, entries 5 and 6), with an overall increase in the mass recovery

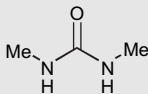
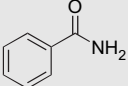
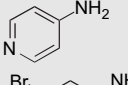
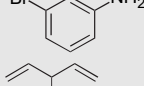
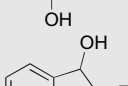
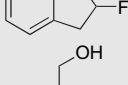
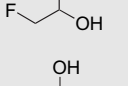
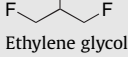
relative to that obtained using benzyl alcohol. Further decreases in *pK<sub>a</sub>* were detrimental: we observed no apparent consumption of the starting butadienoate when the additive was 2-bromoethanol, 2,2-dichloroethanol, 2,2,2-trichloroethanol, or 2,2,2-trifluoroethanol (Table 1, entries 7–10). The use of mismatched alkyl ester and additive alkoxides resulted in mixtures of products through transesterification and the potential addition of two Michael donors; subsequently, we found that the application of matched 2-chloroethyl- and 2-fluoroethyl-2,3-butadienoates resulted in single dihydropyrone products with similar efficiencies (Table 1, entries 11 and 12). In addition to alcohols, we screened an assortment of other Brønsted-acidic additives having values of *pK<sub>a</sub>* within the desirable range (Table 1, entries 13–22); disappointingly, only *N,N'*-dimethylurea and water produced the dihydropyrone product, but with diminished yields and mass recoveries. Due to their promising mix of *pK<sub>a</sub>* and nucleophilicity, we subjected the 2-chloroethanol and 2-fluoroethanol additives to further evaluation. The structural connectivity of dihydropyrone product was established unequivocally through X-ray crystallography of 6-(4-bromophenyl)-4-(2-fluoroethyl)-5,6-dihydro-2*H*-pyran-2-one (Fig. 1).<sup>23</sup>

Next, we further optimized the reaction parameters for the 2-chloroethyl and 2-fluoroethyl butadienoates (Table 2). Diminished yields of the desired dihydropyrone were observed when using tributylphosphine and triethylphosphine as catalysts (Table 2, entries 1 and 2), perhaps due to their increased steric bulk, relative to that of trimethylphosphine, being detrimental to the requisite Michael addition of the alcohol. Trimethylphosphine was the optimal catalyst for the coupling of 3-chlorobenzaldehyde with 2-chloroethyl allenoate (Table 2, entry 3). Unexpectedly, triphenylphosphine also induced dihydropyrone formation, albeit with diminished yield (Table 2, entry 4). This result is notable because it is the first example of triphenylphosphine facilitating the coupling between a butadienoate and an aldehyde. Additionally, in this case we observed no non-cyclic product, presumably because a decrease in rate of the Michael addition/elimination step allowed lactonization to compete effectively with catalyst regeneration. From a solvent screening evaluation, the optimal solvent was dichloromethane, which combined an increase in efficiency with a higher yield of cyclized product (Table 2, cf. entry 5 with entries 6–11 for other common organic solvents). We believe that the favorable outcome with non-polar solvents is the result of more-efficient association of the alcohol additives with the zwitterionic intermediates. In dichloromethane, the combination of 2-fluoroethyl allenoate and 2-fluoroethanol furnished a higher yield of the dihydropyrone as well as better ratio with respect to the non-cyclic product (Table 2, entry 12). Interestingly, the yield increased further when using triphenylphosphine as the catalyst; more importantly, no non-cyclic product was formed (57%; Table 2, entry 13).

With the choice of catalyst, solvent, and Brønsted acid additive optimized, we proceeded to probe the scope of the formation of dihydropyrone (Table 3). In the hope of reducing the degree of undesirable allenoate oligomerization as a side reaction limiting the mass recovery, the 0.25 M butadienoate solution was added slowly. Benzaldehydes presenting a variety of electron-withdrawing substituents provided their dihydropyrone in good yields (Table 3, entries 1–5). Interestingly, trimethylphosphine proved to be a more effective catalyst for some substrates, such as the trifluoromethyl-substituted benzaldehydes (Table 3, entries 6 and 7). As demonstrated in previous allene/aldehyde annulations,<sup>12</sup> electron-rich aromatic aldehydes exhibited low efficiencies (entries 8–11). A heteroaromatic substrate, 3-pyridine carboxaldehyde, was also compatible with the optimized reaction conditions, providing the corresponding substituted pyridine in 68% yield (entry 12). Disubstituted dihydropyrone were obtained rapidly in a single

**Table 1**  
Screening of various hydrogen-bond-donating additives



Entry	R <sup>1</sup>	R <sup>2</sup> or additive	pK <sub>a</sub> of R <sup>2</sup> OH in H <sub>2</sub> O (DMSO) <sup>a</sup>	Yield <sup>b</sup> (%; <b>4</b> / <b>8</b> / <b>2</b> )
1	<i>i</i> -Pr	<i>i</i> -Pr	16.5 (30.3)	54 (16:0:84)
2	Et	Et	16.0 (29.8)	70 (23:21:55)
3	Me	Me	15.5 (29.0)	78 (54:39:7)
4	Bn	Bn	15.2, 15.4	36 (100:0:0)
5	Me	CH <sub>2</sub> CH <sub>2</sub> Cl	14.3	55 (90:10:0) <sup>d</sup>
6	Me	CH <sub>2</sub> CH <sub>2</sub> F	13.9, 14.2	49 (85:15:0) <sup>d</sup>
7	<i>i</i> -Pr	CH <sub>2</sub> CH <sub>2</sub> Br	13.8	0
8	Me	CH <sub>2</sub> CHCl <sub>2</sub>	12.9	Trace
9	Me	CH <sub>2</sub> CCl <sub>3</sub>	11.8, 12.2	0
10	Me	CH <sub>2</sub> CF <sub>3</sub>	11.4, 12.4 (23.5)	0
11	CH <sub>2</sub> CH <sub>2</sub> Cl	CH <sub>2</sub> CH <sub>2</sub> Cl	14.3	41 (81:19:0)
12	CH <sub>2</sub> CH <sub>2</sub> F	CH <sub>2</sub> CH <sub>2</sub> F	13.9, 14.2	51 (89:11:0)
13	Me	H <sub>2</sub> O	15.7 (31.4)	31 (46:4:50) <sup>e</sup>
14	Me		14.6 (26.9) <sup>f</sup>	11 (100:0:0) <sup>e</sup>
15	Me		14.5 (23.3)	0
16	CH <sub>2</sub> CH <sub>2</sub> Cl		(26.5)	0
17	CH <sub>2</sub> CH <sub>2</sub> F		(28.4)	0
18	CH <sub>2</sub> CH <sub>2</sub> F		13.7	0
19	CH <sub>2</sub> CH <sub>2</sub> F		13.0	0
20	CH <sub>2</sub> CH <sub>2</sub> F		13.1	0
21	CH <sub>2</sub> CH <sub>2</sub> F		12.7	0
22	<i>i</i> -Pr	Ethylene glycol	14.77	Decomposition

<sup>a</sup> Data collected from Ref. 24; if two sources report slightly different pK<sub>a</sub> values in water, both values are provided.<sup>24</sup>

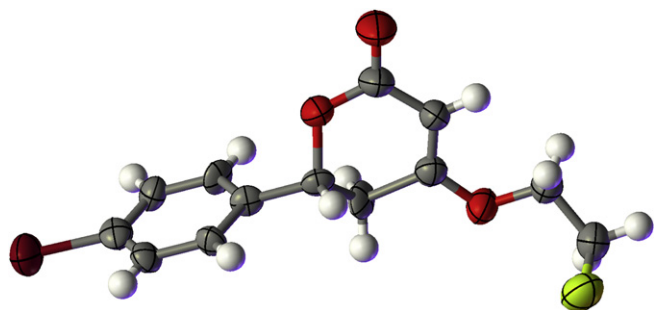
<sup>b</sup> Isolated yields.

<sup>c</sup> The alkene stereochemistry was exclusively *E* (NOESY NMR spectroscopy).

<sup>d</sup> Both methoxide and the 2-haloethoxide were incorporated as β-substituents (OR<sup>2</sup>) in **4** and **8**.

<sup>e</sup> Methoxide incorporated as the β-substituent.

<sup>f</sup> Value of pK<sub>a</sub> for urea in DMSO.

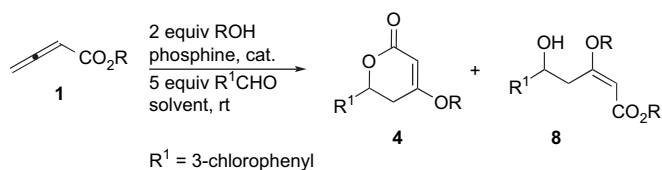


**Figure 1.** X-ray crystallographic representation of 6-(4-bromophenyl)-4-(2-fluoroethyl)-5,6-dihydro-2H-pyran-2-one **4i**.

step from simple, bench-stable starting materials in moderate to good yields.

### 3. Conclusion

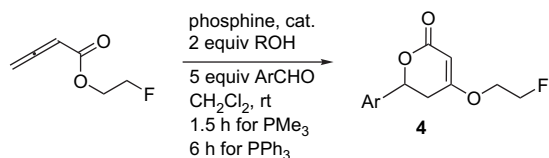
We have uncovered a new mode for the phosphine-catalyzed reaction of 2,3-butadienoates with aromatic aldehydes, namely the formation of disubstituted dihydropyrones, through the addition of Brønsted-acidic additives, which presumably interact with the zwitterionic β-phosphonium dienolate **5**, shifting the equilibrium toward its *s-cis* isomer. Previously, such a shift had required the use of an extremely bulky phosphine catalyst, which inhibited Michael addition of an alkoxide, resulting instead in the formation of pyrone products. Using an additive, in addition to a nucleophilic phosphine

**Table 2**  
Screening of solvents and phosphine catalysts

Entry	R	Solvent	Phosphine <sup>a</sup>	Yield <sup>b</sup> (%; <b>4/8</b> ) <sup>c</sup>
1	CH <sub>2</sub> CH <sub>2</sub> Cl	CHCl <sub>3</sub>	P( <i>n</i> -Bu) <sub>3</sub>	0
2	CH <sub>2</sub> CH <sub>2</sub> Cl	CHCl <sub>3</sub>	PEt <sub>3</sub>	15 (100:0)
3	CH <sub>2</sub> CH <sub>2</sub> Cl	CHCl <sub>3</sub>	PMe <sub>3</sub>	41 (81:19)
4	CH <sub>2</sub> CH <sub>2</sub> Cl	CHCl <sub>3</sub>	PPh <sub>3</sub>	18 (100:0)
5	CH <sub>2</sub> CH <sub>2</sub> Cl	CH <sub>2</sub> Cl <sub>2</sub>	PMe <sub>3</sub>	48 (88:13)
6	CH <sub>2</sub> CH <sub>2</sub> Cl	DCE	PMe <sub>3</sub>	31 (86:14)
7	CH <sub>2</sub> CH <sub>2</sub> Cl	Benzene	PMe <sub>3</sub>	29 (86:14)
8	CH <sub>2</sub> CH <sub>2</sub> Cl	Toluene	PMe <sub>3</sub>	28 (84:16)
9	CH <sub>2</sub> CH <sub>2</sub> Cl	Et <sub>2</sub> O	PMe <sub>3</sub>	12 (100:0)
10	CH <sub>2</sub> CH <sub>2</sub> Cl	THF	PMe <sub>3</sub>	8 (100:0)
11	CH <sub>2</sub> CH <sub>2</sub> Cl	DMF	PMe <sub>3</sub>	0
12	CH <sub>2</sub> CH <sub>2</sub> F	CH <sub>2</sub> Cl <sub>2</sub>	PMe <sub>3</sub>	51 (89:11)
13	CH <sub>2</sub> CH <sub>2</sub> F	CH <sub>2</sub> Cl <sub>2</sub>	PPh <sub>3</sub>	57 (100:0)

<sup>a</sup> Trialkylphosphine: 26 mol %; PPh<sub>3</sub>: 20 mol %.<sup>b</sup> Isolated yields.<sup>c</sup> The alkene stereochemistry was exclusively *E* (NOESY NMR spectroscopy).

catalyst, to induce an alternate reaction pathway is an example of dual activation of the starting material substrates. Adjustment of the pK<sub>a</sub> and nucleophilicity of the additives was necessary to prevent formation of non-cyclized products, which formed presumably through premature catalyst regeneration; 2-fluoroethyl butadienoate and 2-fluoroethanol were the optimal substrate and additive. Additionally, the use of triphenylphosphine as the catalyst led to complete inhibition of the non-cyclized product, possibly due to a reduction in rate of Michael addition of the alkoxide so that complete lactonization could occur. The dual activation present in the mechanism of this reaction pathway suggests many avenues for chiral induction: e.g., bifunctional catalysts featuring both hydrogen-bond-donating and nucleophilic reaction sites, asymmetric phosphine catalysts, or chiral Brønsted-acidic additives. In addition, increasing the allenolate's complexity through either  $\alpha$ - or  $\gamma$ -substitution would increase the complexity of the resultant dihydropyrones.

**Table 3**  
Syntheses of various 6-aryl-4-(2-fluoroethoxy)-5,6-dihydro-2-pyrones<sup>a</sup>

Entry	Ar	Phosphine <sup>b</sup>	Product	Yield (%) <sup>c</sup>
1	4-NCC <sub>6</sub> H <sub>4</sub>	PPh <sub>3</sub>	<b>4a</b>	81
2	3-NCC <sub>6</sub> H <sub>4</sub>	PPh <sub>3</sub>	<b>4b</b>	72
3	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	PPh <sub>3</sub>	<b>4c</b>	77
4	3-ClC <sub>6</sub> H <sub>4</sub>	PPh <sub>3</sub>	<b>4d</b>	61
5	4-AcC <sub>6</sub> H <sub>4</sub>	PPh <sub>3</sub>	<b>4e</b>	58
6	4-F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	PMe <sub>3</sub>	<b>4f</b>	58
7	2-F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	PMe <sub>3</sub>	<b>4g</b>	55
8	C <sub>6</sub> H <sub>5</sub>	PMe <sub>3</sub>	<b>4h</b>	30
9	4-BrC <sub>6</sub> H <sub>4</sub>	PMe <sub>3</sub>	<b>4i</b>	40
10	3-MeC <sub>6</sub> H <sub>4</sub>	PMe <sub>3</sub>	<b>4j</b>	21
11	3-MeOC <sub>6</sub> H <sub>4</sub>	PMe <sub>3</sub>	<b>4k</b>	39
12	3-Pyridyl	PMe <sub>3</sub>	<b>4l</b>	68

<sup>a</sup> Dilute allenolate addition; see Section 4 for a detailed procedure.<sup>b</sup> PPh<sub>3</sub>: 20 mol %; PMe<sub>3</sub>: 25 mol %.<sup>c</sup> Isolated yield.

## 4. Experimental

### 4.1. General

All reactions were performed under an argon atmosphere with dry solvents and anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium/benzophenone ketyl; dichloromethane, benzene, and toluene were freshly distilled from CaH<sub>2</sub>. All other anhydrous solvents were packaged in Sure/Seal™ bottles and were used as received from Aldrich; chloroform was further distilled from calcium chloride immediately prior to use. All the aldehydes were commercially available and purchased from Aldrich or Acros Organics. The liquid aldehydes were washed sequentially with saturated sodium bicarbonate and saturated sodium chloride and then distilled prior to use. Solid aldehydes were dissolved in dichloromethane, washed with saturated sodium bicarbonate, evaporated to dryness, and then stored under vacuum over phosphorus pentoxide. All the phosphines were commercially available and purchased from Aldrich, Strem Chemicals, Inc., Organometallics, Inc., or Maybridge Chemicals. All other reagents were used as received from commercial sources, with the alcohols stored over 4 Å molecular sieves. Reactions were monitored through thin layer chromatography (TLC) on 0.25-mm Silicycle silica gel plates (TLG-R10011B-323), visualizing with UV light or staining with permanganate or anisaldehyde. Flash column chromatography was performed using Silicycle Silia-P gel (50- $\mu$ m particle size, R12030B) and compressed air. IR spectra were recorded on a Perkin–Elmer Paragon1000 FT-IR spectrometer. NMR spectra were obtained on a Bruker Avance-500 instrument and calibrated using residual non-deuterated chloroform as an internal reference (7.26 ppm for <sup>1</sup>H NMR; 77.00 ppm for <sup>13</sup>C NMR). Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift ( $\delta$  ppm), multiplicity, coupling constant (Hz), and integration. Data for <sup>13</sup>C NMR spectra are reported in terms of chemical shift and multiplicities, with coupling constants (Hz) in the case of J<sub>CF</sub> coupling. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad; and app, apparent. High-resolution electrospray ionization/time of flight (ESI-TOF) mass spectrometry data were collected on a QStar Elite Hybrid LC/MS/MS system, with caffeine and MRFA peptide (methionine-arginine-phenylalanine-alanine) peptide used as internal calibration standards.

### 4.2. General procedure for the synthesis of dihydropyrones

Dry solvent (10 mL) was added to a flame-dried, 15-mL round-bottom flask under an argon atmosphere, followed by the neat aldehyde (5.0 equiv), the alcohol additive (2.0 equiv), and the phosphine (20 mol % for PPh<sub>3</sub>; 26 mol % for PMe<sub>3</sub>); in the case of a solid phosphine, additive, or aldehyde, the compound was added prior to the solvent and the argon was replenished. Using a 250- $\mu$ L micro syringe, the allenolate (1.0 mmol) was added dropwise over a period of 30 min. An orange-red solution was obtained; the mixture was stirred at room temperature until TLC (eluant: 20% EtOAc/hexanes; permanganate stain) revealed consumption of the allenolate. The reaction mixture was concentrated and the residue purified through flash column chromatography (SiO<sub>2</sub>; 33–50% EtOAc/hexanes) to give the products.

#### 4.2.1. 4-Benzoyloxy-6-(3-chlorophenyl)-5,6-dihydro-2H-pyran-2-one

Yield 36%; thick oil; IR (neat)  $\nu_{\max}$  1700, 1622, 1558, 1540, 1506, 1472, 1456, 1224 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.44–7.28 (m, 9H), 5.44 (dd, *J* = 12.2, 3.8 Hz, 1H), 5.36 (d, *J* = 1.5 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 2H), 2.84 (ddd, *J* = 17.0, 12.0, 1.5 Hz, 1H), 2.68 (dd, *J* = 17.0, 4.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 166.2, 140.1, 134.6,



134.1, 129.9, 128.8, 128.7, 127.8, 126.1, 123.9, 91.6, 76.2, 71.1, 35.0; MS (ESI-TOF) calcd for  $C_{18}H_{16}O_3Cl^+ [M+H]^+$  315.0788, found 315.0782.

### 4.3. Optimized experimental procedure for the synthesis of dihydropyrones

Dry solvent (8 mL) was added to a flame-dried, 15-mL round-bottom flask under an argon atmosphere, followed by the neat aldehyde (5.0 equiv), the alcohol additive (2.0 equiv), and the phosphine (20 mol% for  $PPh_3$ ; 26 mol% for  $PMe_3$ ); in the case of a solid phosphine, additive, or aldehyde, the compound was added prior to the solvent and then the argon was replenished. A solution of the allenolate (1 mmol) in dry solvent (4 mL) was added over 30 min using a syringe pump. An orange-red solution was obtained; the mixture was stirred at room temperature until TLC (eluant: 20% EtOAc/hexanes; permanganate stain) revealed consumption of the allenolate. The reaction typically took 1.5 h for  $PMe_3$  and 6 h for  $PPh_3$ . The reaction mixture was concentrated and the residue purified through flash column chromatography ( $SiO_2$ ; 33–50% EtOAc/hexanes) to give the products. Spectral data for the new dihydropyrones listed in Table 3 are provided below.

#### 4.3.1. 6-(4-Cyanophenyl)-4-(2-fluoroethoxy)-5,6-dihydro-2H-pyran-2-one (4a)

Yield 80.8%; white solid; IR (neat)  $\nu_{max}$  1712, 1626, 1391, 1228, 1076, 918, 835, 583  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.71 (dd,  $J=6.8, 1.7$  Hz, 2H), 7.55 (d,  $J=8.5$  Hz, 2H), 5.50 (dd,  $J=11.8, 4.2$  Hz, 1H), 5.26 (d,  $J=1.5$  Hz, 1H), 4.73 (dt,  $J=47.5, 4.0$  Hz, 2H), 4.25–4.10 (m, 2H), 2.81 (ddd,  $J=17.0, 12.0, 1.5$  Hz, 1H), 2.71 (dd,  $J=17.3, 4.3$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.6, 165.6, 143.1, 132.5, 126.4, 118.2, 112.6, 91.5, 80.4 ( $J_{CF}=172$  Hz), 75.9, 68.0 ( $J_{CF}=20$  Hz), 34.7; MS (ESI-TOF) calcd for  $C_{14}H_{13}O_3NF [M+H]^+$  262.0879, found 262.0873.

#### 4.3.2. 6-(3-Cyanophenyl)-4-(2-fluoroethoxy)-5,6-dihydro-2H-pyran-2-one (4b)

Yield 72.3%; white solid; IR (neat)  $\nu_{max}$  1710, 1621, 1392, 1294, 1235, 1191, 1072, 1021  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.74 (s, 1H), 7.68 (t,  $J=6.5$  Hz, 2H), 7.54 (t,  $J=8.0$  Hz, 1H), 5.48 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.27 (d,  $J=1.5$  Hz, 1H), 4.74 (dt,  $J=47.5, 4.0$  Hz, 2H), 4.26–4.11 (m, 2H), 2.83 (ddd,  $J=17.0, 12.0, 1.5$  Hz, 1H), 2.71 (dd,  $J=17.5, 4.0$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.6, 165.5, 139.6, 132.2, 130.1, 129.6, 129.4, 118.1, 113.0, 91.5, 80.43 ( $J_{CF}=172$  Hz), 75.7, 68.0 ( $J_{CF}=20$  Hz), 34.7; MS (ESI-TOF) calcd for  $C_{14}H_{13}O_3NF [M+H]^+$  262.0879, found 262.0880.

#### 4.3.3. 4-(2-Fluoroethoxy)-6-(3-nitrophenyl)-5,6-dihydro-2H-pyran-2-one (4c)

Yield 77.0%; white solid; IR (neat)  $\nu_{max}$  1715, 1625, 1532, 1353, 1228, 1074, 816, 740  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.31 (t,  $J=1.5$  Hz, 1H), 8.24 (d,  $J=8.0$  Hz, 1H), 7.80 (t,  $J=8.0$  Hz, 1H), 7.62 (t,  $J=8.0$  Hz, 1H), 5.56 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.29 (d,  $J=1.5$  Hz, 1H), 4.74 (dt,  $J=47.0, 4.0$  Hz, 2H), 4.27–4.12 (m, 2H), 2.88 (ddd,  $J=17.3, 12.3, 1.5$  Hz, 1H), 2.76 (dd,  $J=17.3, 4.3$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.6, 165.5, 148.3, 140.1, 131.9, 129.9, 123.6, 120.9, 91.5, 80.5 ( $J_{CF}=172$  Hz), 75.7, 68.1 ( $J_{CF}=20$  Hz), 34.7; MS (ESI-TOF) calcd for  $C_{13}H_{13}O_5NF^+ [M+H]^+$  282.0778, found 282.0772.

#### 4.3.4. 6-(4-Acetylphenyl)-4-(2-fluoroethoxy)-5,6-dihydro-2H-pyran-2-one (4e)

Yield 57.6%; yellow oil; IR (neat)  $\nu_{max}$  1711, 1681, 1625, 1360, 1270, 1227, 1074, 603  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.99 (d,  $J=8.0$  Hz, 2H), 7.52 (d,  $J=8.0$  Hz, 2H), 5.51 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.26 (d,  $J=1.5$  Hz, 1H), 4.73 (dt,  $J=47.0, 4.0$  Hz, 2H), 4.25–4.10 (m, 2H), 2.84 (ddd,  $J=17.0, 12.0, 1.5$  Hz, 1H), 2.71 (dd,  $J=17.0, 4.0$  Hz, 1H), 2.61 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  197.4, 170.8, 165.9, 143.0,

137.2, 128.7, 125.9, 91.5, 80.5 ( $J_{CF}=171$  Hz), 76.4, 67.9 ( $J_{CF}=20$  Hz), 34.8, 26.6; MS (ESI-TOF) calcd for  $C_{15}H_{16}O_4F^+ [M+H]^+$  279.1033, found 279.1027.

#### 4.3.5. 4-(2-Fluoroethoxy)-6-(4-trifluoromethylphenyl)-5,6-dihydro-2H-pyran-2-one (4f)

Yield 57.8%; white solid; IR (neat)  $\nu_{max}$  1713, 1626, 1327, 1228, 1168, 1125, 1068, 1018  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.68 (d,  $J=8.5$  Hz, 2H), 7.55 (d,  $J=8.0$  Hz, 2H), 5.52 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.27 (d,  $J=1.5$  Hz, 1H), 4.74 (dt,  $J=47.5, 4.0$  Hz, 2H), 4.26–4.10 (m, 2H), 2.84 (ddd,  $J=17.0, 12.0, 1.5$  Hz, 1H), 2.72 (dd,  $J=17.0, 4.0$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.8, 165.8, 141.9, 130.8 (q,  $J_{CF}=32$  Hz), 126.1, 125.7 (q,  $J_{CF}=3.8$  Hz), 123.8 (q,  $J_{CF}=270.4$  Hz), 91.5, 80.5 ( $J_{CF}=172$  Hz), 76.2, 68.0 ( $J_{CF}=20$  Hz), 34.8; MS (ESI-TOF) calcd for  $C_{14}H_{13}O_3F_4 [M+H]^+$  305.0801, found 305.0806.

#### 4.3.6. 4-(2-Fluoroethoxy)-6-(2-trifluoromethylphenyl)-5,6-dihydro-2H-pyran-2-one (4g)

Yield 54.9%; white solid; IR (neat)  $\nu_{max}$  1722, 1712, 1626, 1315, 1229, 1165, 1118, 1072  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.85 (d,  $J=7.5$  Hz, 1H), 7.69–7.64 (m, 2H), 7.48 (t,  $J=7.7$  Hz, 1H), 5.82 (dd,  $J=12.5, 4.0$  Hz, 1H), 5.27 (d,  $J=2.0$  Hz, 1H), 4.80–4.68 (dm,  $J=47.0$  Hz, 2H), 4.26–4.21 (m, 2H), 2.79 (ddd,  $J=17.5, 12.5, 1.5$  Hz, 1H), 2.65 (dd,  $J=17.5, 3.8$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  171.0, 166.1, 136.9, 132.4, 128.7, 128.2, 126.9 (q,  $J_{CF}=30$  Hz), 125.6 (q,  $J_{CF}=6$  Hz), 124.0 (q,  $J_{CF}=272$  Hz), 91.2, 80.5 (d,  $J_{CF}=171$  Hz), 73.4, 68.0 (d,  $J_{CF}=20$  Hz), 35.7; MS (ESI-TOF) calcd for  $C_{14}H_{13}O_3F_4 [M+H]^+$  305.0801, found 305.0802.

#### 4.3.7. 4-(2-Fluoroethoxy)-6-phenyl-5,6-dihydro-2H-pyran-2-one (4h)

Yield 30.4%; white solid; IR (neat)  $\nu_{max}$  1726, 1711, 1632, 1223, 1068, 917, 702, 577  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.43–7.34 (m, 5H), 5.45 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.25 (d,  $J=1.5$  Hz, 1H), 4.73 (dt,  $J=47.5, 4.0$  Hz, 2H), 4.24–4.12 (m, 2H), 2.88 (ddd,  $J=17.3, 12.3, 1.5$  Hz, 1H), 2.67 (dd,  $J=17.0, 4.0$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  171.2, 166.4, 138.0, 128.6, 128.6, 125.9, 91.4, 80.57 ( $J_{CF}=171$  Hz), 77.1, 67.8 ( $J_{CF}=20$  Hz), 34.8; MS (ESI-TOF) calcd for  $C_{13}H_{14}O_3F [M+H]^+$  237.0927, found 237.0927.

#### 4.3.8. 6-(4-Bromophenyl)-4-(2-fluoroethoxy)-5,6-dihydro-2H-pyran-2-one (4i)

Yield 40.1%; white solid; IR (neat)  $\nu_{max}$  1704, 1630, 1389, 1347, 1224, 1059, 914, 828, 443  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.53 (d,  $J=8.5$  Hz, 2H), 7.30 (d,  $J=8.5$  Hz, 2H), 5.41 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.24 (d,  $J=1.5$  Hz, 1H), 4.73 (dt,  $J=47.0, 4.0$  Hz, 2H), 4.24–4.09 (m, 2H), 2.82 (ddd,  $J=17.5, 12.0, 1.5$  Hz, 1H), 2.66 (dd,  $J=17.5, 4.0$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  171.0, 166.1, 137.1, 131.9, 127.6, 122.7, 91.5, 80.6 (d,  $J_{CF}=171$  Hz), 76.4, 68.0 (d,  $J_{CF}=20$  Hz), 34.5; MS (ESI-TOF) calcd for  $C_{13}H_{13}O_3FBr^+ [M+H]^+$  315.0032, found 315.0026.

#### 4.3.9. 4-(2-Fluoroethoxy)-6-(3-tolyl)-5,6-dihydro-2H-pyran-2-one (4j)

Yield 21.3%; white solid; IR (neat)  $\nu_{max}$  1711, 1625, 1391, 1291, 1225, 1072, 924, 885  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.30–7.25 (m, 2H), 7.18 (t,  $J=9.0$  Hz, 2H), 5.42 (dd,  $J=12.0, 4.0$  Hz, 1H), 5.24 (d,  $J=2.0$  Hz, 1H), 4.74 (dt,  $J=47.5, 4.0$  Hz, 2H), 4.24–4.09 (m, 2H), 2.87 (ddd,  $J=17.0, 12.0, 1.5$  Hz, 1H), 2.66 (dd,  $J=17.0, 4.0$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  171.2, 166.5, 138.4, 137.9, 129.3, 128.5, 126.6, 122.9, 91.4, 80.5 ( $J_{CF}=171$  Hz), 77.1, 67.8 ( $J_{CF}=20$  Hz), 34.9, 21.3; MS (ESI-TOF) calcd for  $C_{14}H_{16}O_3F [M+H]^+$  251.1083, found 251.1083.

#### 4.3.10. 6-(3-Anisyl)-4-(2-fluoroethoxy)-5,6-dihydro-2H-pyran-2-one (4k)

Yield 39.1%; white solid; IR (neat)  $\nu_{max}$  1710, 1624, 1458, 1392, 1226, 1045, 924, 884  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.31 (t,

$J=8.3$  Hz, 1H), 6.98–6.96 (m, 2H), 6.90 (dd,  $J=8.5$ , 2.0 Hz, 1H), 5.43 (dd,  $J=12.0$ , 4.0 Hz, 1H), 5.24 (d,  $J=1.5$  Hz, 1H), 4.73 (dt,  $J=47.0$ , 4.0 Hz, 2H), 4.24–4.10 (m, 2H), 3.83 (s, 3H), 2.87 (ddd,  $J=17.3$ , 12.3, 1.5 Hz, 1H), 2.67 (dd,  $J=17.0$ , 4.0 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 166.4, 159.8, 139.5, 129.7, 118.0, 114.2, 111.3, 91.4, 80.5 ( $J_{\text{CF}}=171$  Hz), 76.9, 67.8 ( $J_{\text{CF}}=20.4$  Hz), 55.2, 34.9; MS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_4\text{F}^+ [\text{M}+\text{H}]^+$  267.1033, found 267.1023.

#### 4.3.11. 4-(2-Fluoroethoxy)-6-(3-pyridyl)-5,6-dihydro-2H-pyran-2-one (4I)

Yield 68.4%; yellow oil; IR (neat)  $\nu_{\text{max}}$  1710, 1622, 1392, 1228, 1076, 1023, 916, 820  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (d,  $J=2.0$  Hz, 1H), 8.63 (dd,  $J=4.5$ , 1.5 Hz, 1H), 7.83 (dt,  $J=8.0$ , 1.8 Hz, 1H), 7.38 (dd,  $J=8.0$ , 4.5 Hz, 1H), 5.55 (dd, 12.5, 4.0 Hz, 1H), 5.31 (d,  $J=1.5$  Hz, 1H), 4.74 (dt,  $J=47.0$ , 4.0 Hz, 2H), 4.26–4.11 (m, 2H), 2.89 (ddd,  $J=17.0$ , 12.0, 1.5 Hz, 1H), 2.71 (dd, 17.5, 4.0 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 165.8, 150.0, 147.4, 133.8, 133.7, 123.6, 91.5, 80.4 ( $J_{\text{CF}}=171.5$  Hz), 74.8, 68.0 ( $J_{\text{CF}}=20$  Hz), 34.5; MS (ESI-TOF) calcd for  $\text{C}_{12}\text{H}_{13}\text{O}_3\text{NF} [\text{M}+\text{H}]^+$  238.0879, found 238.0868.

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20. It is noted that an energetically less favorable twisted-dienolate minimum, originating from MeOH-mediated hydrogen bond stabilization, possessing a conjugated  $\pi$ -system perturbed from what is an optimal *syn*-periplanar geometry was obtained from this PES-study. The reaction barrier for aldehyde addition to this intermediate was, however, calculated to be more endergonic than the aldehyde addition modes computed to date for **5** and **5a**; consequently, it does not contribute to a productive pathway.
21. We are currently investigating the subsequent aldehyde addition to elucidate the complete mechanism of dihydropyrone formation.
22. The non-cyclized product, once isolated, did not undergo equilibration or cyclization when subjected to the reaction conditions.
23. Crystallographic data (excluding structure factors) for compound **4i** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 675758. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223-336033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).
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