Racemic hemiacetals as oxygen-centered pronucleophiles triggering cascade 1,4-addition/ Michael reaction through dynamic kinetic resolution under iminium catalysis. Development and mechanistic insights†

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2-Hydroxydihydropyran-5-ones behave as excellent polyfunctional reagents able to react with enals through oxa-Michael/Michael process cascade under the combination of iminium and enamine catalysis. These racemic hemiacetalic compounds are used as unconventional O-pronucleophiles in the initial oxa-Michael reaction, also leading to the formation of a single stereoisomer under a dynamic kinetic resolution (DKR) process. Importantly, by using β-aryl or β-alkyl substituted α,β-unsaturated substrates as initial Michael acceptors either kinetically or thermodynamically controlled diastereoisomers were formed with high stereoselection through the careful selection of the reaction conditions. Finally, a complete experimental and computational study confirmed the initially proposed DKR process during the catalytic oxa-Michael/Michael cascade reaction and also explained the kinetic/thermodynamic pathway operating in each case.

Introduction

The asymmetric conjugate addition of heteroatom-centered nucleophiles to α,β-unsaturated carbonyl compounds is one of the leading strategies for the enantio- and/or diastereoselective preparation of β-functionalized carbonyl compounds.1 Moreover, the mechanistic profile associated to the conjugate addition reaction makes this transformation an excellent platform to develop cascade reactions.2 This opens the possibility for the construction of complex molecular architectures from simple starting materials. With respect to stereocontrol, enantioselective catalysis, and more specifically, the proven ability of chiral secondary amines3 to promote cascade reactions using enals as Michael acceptors, through the combination of the nowadays well established iminium and enamine activation manifolds is a good example of the high level of sophistication achieved by this chemistry.4

In this sense, many examples of enantioselective cascade processes triggered by hetero-Michael reactions exist in the literature,5 although reactions initiated by the conjugate addition of oxygen-centered nucleophiles remain scarce.6 In fact, this type of reactions still represent one of the most challenging cases of conjugate addition of heteroatom-centered nucleophiles under organocatalytic activation because, in addition to reversibility issues, the typical oxygen-centered pronucleophiles, such as alcohols or carboxylic acids, typically show very poor reactivity towards Michael acceptors and normally undergo competitive 1,2-addition. Consequently, the reported examples of organocatalytic and enantioselective conjugate addition of oxygen pronucleophiles are limited to the use of oximes,7 phenols,8 enols,9 alkoxycarbenes,10 hydroxylamines,11 or peroxides12 under iminium or H-bonding activation.13 Organocatalytic cascade processes initiated by conjugate addition of O-nucleophiles have been mainly focused on the epoxidation of α,β-unsaturated carboxyls with peroxides14 and some limited examples of conjugate addition followed by aldol,15 Mannich,16 Henry,17 α-amination18 and α-fluorination19 have also been published. However, with respect to 1,4-addition/Michael cascade processes, all cases reported are strictly limited to the use of aliphatic alcohols or phenols as oxygen-centered pronucleophiles (Scheme 1).20

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization of all new compounds, including copies of NMR spectra and HPLC chromatograms traces, computational details and Cartesian coordinates of all stationary points. CCDC 1525188 (4J), 1525189 (6a) and 1525190 (9a). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc00009j
Consequently, we have focused our attention in the use of hemiacetals as potential pronucleophiles in cascade reactions initiated by 1,4-addition. Hemiacetals play a critical role in the chemistry of living cells and this type of compounds is also known to play the role of $O$-pronucleophiles in biochemical pathways of the secondary metabolism. In particular, the intramolecular conjugate addition of hemiacetals is typically associated with the stereodefined formation of acetal moieties in the total synthesis of complex natural products with relevant biological activities. Remarkably, there is only one single example (a diastereoselective approach) that involves the use of a enantioenriched hemiacetal as Michael donor, performing with moderate stereocontrol. On the other hand, the intramolecular conjugate addition of in situ generated hemiacetals using functionalized Michael acceptors that incorporate an internal alcohol moiety to assist the reaction has also been reported in both diastereoe- and enantioselective fashion, although the latter relies on the stereocontrolled formation of the chiral hemiacetal moiety under catalyst control, that subsequently undergoes the intramolecular O-1,4-addition reaction. Finally, and quite recently, the catalytic and enantioselective intramolecular conjugate addition of peroxylhemiacetals to dienones has also been described. Despite these advances, the conjugate addition of hemiacetals to electron-poor alkenes in an intermolecular fashion to initiate a cascade reaction is unprecedented in the chemical literature.

In particular, we wish to present herein a detailed study regarding the ability of hydroxypyranone 1 as an active chiral racemic $O$-pronucleophile that undergoes diastereo- and enantioselective cascade, 1,4-addition/intramolecular Michael reaction with $\alpha,\beta$-unsaturated aldehydes in the presence of a chiral secondary amine catalyst, leading to the formation of bicyclic furo[2,3-$b$]pyranes in a single step (Scheme 2). As far as we are aware of, this is the first example in which a hemiacetal shows its ability to participate as oxygen-based Michael donor in a stereoselective conjugate addition reaction under the combination of iminium and enamine activation manifolds. Moreover, this transformation occurs with the concomitant generation of up to four stereogenic centers in stereocontrolled way using a racemic starting material, in which a dynamic kinetic resolution (DKR) has also taken place to furnish the final adducts as highly enantio- and diastereoenriched compounds.

**Results and discussion**

Our studies began by surveying reaction conditions for the projected transformation to proceed with the best yield and stereoselectivity employing ($E$)-cinnamaldehyde as model substrate (Table 1). We first tested the performance of the well-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield ($%$)</th>
<th>$4a$ : $5a$ ($%$)</th>
<th>ee ($%$)</th>
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<tr>
<td>1</td>
<td>3a</td>
<td>CHCl$_3$</td>
<td>60</td>
<td>1 : 1 : 3</td>
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<td>2</td>
<td>3b</td>
<td>CHCl$_3$</td>
<td>&lt;5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>None</td>
<td>43</td>
<td>1 : 2 : 3</td>
<td>n.d.$^c$/38/50</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>CHCl$_3$</td>
<td>46</td>
<td>1 : 1 : 3</td>
<td>90/60/95</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>DABCO</td>
<td>67</td>
<td>1 : 1 : 1</td>
<td>90/78/90</td>
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<td>6</td>
<td>3a</td>
<td>CHCl$_3$</td>
<td>80</td>
<td>2 : 1 : 2</td>
<td>67/67/95</td>
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<td>7</td>
<td>3a</td>
<td>CHCl$_3$</td>
<td>74</td>
<td>&lt;0.2 : 1 : 4</td>
<td>n.d.$^c$/60/92</td>
</tr>
<tr>
<td>8</td>
<td>3d</td>
<td>CHCl$_3$</td>
<td>&lt;5</td>
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<td>—</td>
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<td>9</td>
<td>3a</td>
<td>Toluene</td>
<td>62</td>
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<td>n.d.$^c$/20/94</td>
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<tr>
<td>10</td>
<td>3a</td>
<td>CH$_2$Cl$_2$</td>
<td>43</td>
<td>&lt;0.2 : 1 : 3</td>
<td>n.d.$^c$/38/90</td>
</tr>
<tr>
<td>11$^{la}$</td>
<td>3a</td>
<td>CHCl$_3$</td>
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<td>&lt;0.2 : 1 : 2</td>
<td>n.d.$^c$/60/95</td>
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<tr>
<td>12$^{la}$</td>
<td>3a</td>
<td>CHCl$_3$</td>
<td>75</td>
<td>&lt;0.2 : 1 : 4</td>
<td>n.d.$^c$/64/93</td>
</tr>
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</table>

$^a$ Reactions were carried out using 0.4 mmol of 1 and 0.2 mmol of 2a, 20 mol% of catalyst 3 and 10 mol% of additive in 0.8 mL of CHCl$_3$ at rt for 18 h, followed by direct purification by flash chromatography. Combination yield for the mixture of diastereoisomers. $^c$ Determined by $^1$H NMR spectroscopy of crude reaction mixture. $^d$ Determined by HPLC after derivatization (see ESI). $^e$ n.d.: not determined. $^f$ Once the reaction was finished a 4 M HCl solution (2.0 mL) was added to the crude reaction mixture and this was stirred for further 4 h before standard work-up and purification. $^g$ Reaction carried out at 4 °C. $^h$ Reaction carried out at 45 °C.

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**Table 1** Optimization of reaction conditions using hydroxypyranone 1 and aldehyde 2a as model substrates

**Scheme 1** Organocatalytic cascade processes initiated by conjugate addition of $O$-nucleophiles.

**Scheme 2** Enantioselective oxa-Michael/Michael cascade reaction between enals and hydroxypyranone 1.
known O-TMS diphenylprolinol catalyst 3a,\textsuperscript{26} observing the formation of the expected bicyclic furan derivative as a mixture of three diastereoisomers out of the eight possible ones (Table 1, entry 1). An analysis of their stereostructure\textsuperscript{27} showed that the reaction had proceeded with complete control at the C2 stereocenter, which indicated that the catalyst was able to perfectly control the facial selectivity in the initial 1,4-addition reaction. Compounds 4a and 6a differ on the absolute configuration of the stereochemically labile C3 stereocenter, assuming that the latter was formed after thermodynamic epimerization of the former (a detailed discussion will be provided in the following sections). Finally, the presence of diastereoisomer 5a should be ascribed to the participation of the other enantiomer of the racemic starting material 1. It should be noted that an excess of hemiacetal 1 was used in order to achieve full conversion after 18 h but when the reaction was carried out using equimolar amounts of 1 and 2, it proceeded with exactly the same diastereo- and enantiocontrol.\textsuperscript{28} Moreover, in all cases, the recovered starting material 1 was found to be racemic. Consequently, the observed yield, the high (6a + 4a)/5a ratio and the excellent e.e. obtained for 6a is indicating that a kinetic resolution is operating throughout the overall reaction, which encouraged us to search for improved conditions that could favour the selective formation of major diastereoisomer 6a. Consequently, we next tested the performance of modified catalyst 3b (entry 2), but it was found to be inactive in this transformation, while the use of less bulky O-Me derivative 3c turned into poorer enantiocontrol for the major product 6a (entry 3). The incorporation of Bronsted acids or bases as additives did not end up in any significant improvement (entries 4 and 5). Remarkably, using achiral thiourea 7 as co-catalyst, which had been previously used by us for the activation of Michael acceptors in reactions under dienamine activation,\textsuperscript{29} led to an important improvement in the yield of the reaction (entry 6). In addition, the formation of 4a could be minimized by stirring the crude reaction mixture with aqueous HCl for 4 h to favour the thermodynamic equilibration of the 4a/6a mixture (entry 7). We also tested bifunctional catalyst 3d, not observing better results (entry 8). Other solvents (entries 9 and 10) and temperatures (entries 11 and 12) were also surveyed, without observing any significant improvement and therefore, it was concluded that the conditions summarized in entry 7 of Table 1 were the most appropriate ones for this transformation.

With the optimal conditions in hands, the scope of the reaction was studied with respect to the use of other \( \alpha,\beta \)-unsaturated aldehydes 2a-i. As summarized in Table 2, the reaction proceeded well in all cases in which cinnamaldehyde derivatives incorporating either electron-withdrawing or electron-donating groups at the \( \beta \)-aryl substituent were employed (entries 1–7). In all these cases, adducts 6a–g were isolated with good yields, high diastereoselectivities and as highly enantioenriched materials. \( \beta \)-Heteroaryl substituents were also well tolerated, observing that the reaction performed equally well in terms of chemical yield and stereocontrol (entry 8). On the other hand, when we turned to the use of a \( \beta \)-alkyl substituted enal such as 2-hexenal, a 1 : 1 : 2 mixture of the three diastereoisomers was obtained with an overall yield of 87% (entry 9).

Unfortunately, in this case the acidic workup was ineffective for converting diastereoisomer 4i into 6i,\textsuperscript{30} which also indicated that \( \beta \)-alkyl substituted enals behave differently from cinnamaldehyde derivatives with respect to diastereoselection. Remarkably, the formation of diastereoisomer 5 was negligible in all cases, which indicated that the DKR process was operating with high efficiency. We tried to improve the diastereoselectivity of the reaction between 2i and 1, by surveying other conditions but without any success (see ESI for details). Remarkably, when catalyst 3c was employed together with trichloroacetic acid as additive, the reaction again turned to be highly diastereo- and enantioselective, in this case favouring the formation of the kinetic product 4i (entry 10). This product showed to be less prone to C3-epimerization compared with the cases in which \( \beta \)-aryl substituted enals were used and all attempts to induce the 4i to 6i isomerization under acidic or basic conditions led to decomposition.

Once we had realized that \( \beta \)-alkyl substituted enals required the use of catalyst 3c, we proceeded to extend those conditions to a variety of substrates (Table 3). As it can be seen in this table, the reaction tolerates well the use of enals containing alky chains of different length and size, also observing that the yield of the process became only moderately affected when the length of the chain was considerably increased (entries 1–5). Aldehyde 2n containing a bulkier non-linear alky chain also performed well, although enantioselectivity was slightly affected (compound 4n) and a functionalized \( \alpha,\beta \)-unsaturated aldehyde such as 2o also performed well, furnishing 4o in good yield and stereocontrol (entry 7). Furthermore, \( \beta,\beta \)-disubstituted aldehyde 2p was also reactive under these conditions, forming adduct 4p in good yield, although with moderate

### Table 2. Scope of the reaction between cinnamaldehyde derivatives and hydroxypyranone

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (product)</th>
<th>Yield (%)</th>
<th>5 : 6&lt;sup&gt;a&lt;/sup&gt;</th>
<th>c.e. 6&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Ph (6a)</td>
<td>74</td>
<td>1 : 4</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>4-(OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6b)</td>
<td>63</td>
<td>1 : 4</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6c)</td>
<td>73</td>
<td>1 : 2</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4-(NO&lt;sub&gt;2&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6d)</td>
<td>78</td>
<td>1 : 2</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6e)</td>
<td>87</td>
<td>1 : 1.5</td>
<td>88</td>
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<tr>
<td>6</td>
<td>2-(OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6f)</td>
<td>61</td>
<td>1 : 3</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>2-(NO&lt;sub&gt;2&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (6g)</td>
<td>71</td>
<td>1 : 3</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>2-(Furyl) (6h)</td>
<td>64</td>
<td>1 : 10</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>n-Pr (6i)</td>
<td>87</td>
<td>1 : 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>n-Pr (4i)</td>
<td>76</td>
<td>8 : 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>93&lt;sup&gt;f&lt;/sup&gt;</td>
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</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixture.
<sup>b</sup> Determined by HPLC (see ESI).
<sup>c</sup> Reaction also furnished diastereoisomer 4i (4i/5i ratio = 1 : 1 : 2).
<sup>d</sup> Reaction conditions: catalyst 3c (20 mol%), Cl<sub>3</sub>CCO<sub>2</sub>H (40 mol%) in CHCl<sub>3</sub> at rt. 4i/5i ratio is indicated.
<sup>e</sup> c.e. of 4i is given.
diastereoisomer. This reaction involved the activation of the 12k compound. NHC catalysis was also carried out on adducts 1. On the other hand, intramolecular benzoin condensation under acidic conditions with full chemoselectivity considering the presence of two different ketone moieties in adduct 4. For example, the fully protection of the formyl and hydroxypyranone functionalities is shown before, the formation of diastereoisomer 1 could be grown that also allowed the unequivocal assignment of the absolute configuration of the products. The ketone moiety, generating a quaternary carbinol with complete diastereoisolation.

### Mechanistic considerations

In order to get a good mechanistic understanding on the behavior of the reaction, we decided to carry out a detailed experimental and computational study, mainly directed to understand the origin of the difference in the diastereoselectivity of this cascade process when β-aryl or β-alkyl-substituted Michael acceptors were employed as substrates, and also to try to understand the pathway operating in the resolution process, which is key for the very high stereocontrol. In this sense, and considering the presence of multiple reactive positions in the starting materials in which the amine catalyst can incorporate through either covalent bonding or via H-bonding interactions, we firstly carried out some experiments directed to discard the possible participation of complex reaction intermediates in which two or more molecules of the catalyst could be incorporated. In this sense, the process did not show any significant non-linear behavior when the reaction between 1 and 2a using catalyst 3a with a variable enantiopurity (Fig. 1). This is a clear indication that only one molecule of catalyst is involved in the rate determining step of the overall catalytic cycle.

We next moved to study the different mechanistic possibilities with the help of computational methods (for details see ESI†). Firstly, we set a preliminary computational study with an accurate non-linear behavior when the reaction between 1 and 2a using catalyst 3a with a variable enantiopurity (Fig. 1). This is a clear indication that only one molecule of catalyst is involved in the rate determining step of the overall catalytic cycle.

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### Table 3: Scope of the reaction between β-alkyl substituted enals and hydroxypyranone 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1, R2 (product)</th>
<th>Yield (%)</th>
<th>4 : 5a (%)</th>
<th>e.e. (%)</th>
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<tr>
<td>1</td>
<td>n-Pr, H (4i)</td>
<td>76</td>
<td>8 : 1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Et, H (4j)</td>
<td>72</td>
<td>9 : 1</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu, H (4k)</td>
<td>69</td>
<td>11 : 1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>n-C6H13, H (4l)</td>
<td>73</td>
<td>5 : 1</td>
<td>95</td>
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<tr>
<td>5</td>
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<td>61</td>
<td>7 : 1</td>
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<tr>
<td>6</td>
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<td>59</td>
<td>4 : 1</td>
<td>84</td>
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<tr>
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<td>(Z)-EtCH=CH(CH2)2, H (4o)</td>
<td>60</td>
<td>5 : 1</td>
<td>96</td>
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<td>8</td>
<td>Me, Me (4p)</td>
<td>73</td>
<td>2 : 1</td>
<td>77</td>
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</table>

* Determined by 1H NMR spectroscopy of crude reaction mixture.  
** Determined by HPLC (see ESI).  
† Determined by 1H NMR spectroscopy of crude reaction mixture.
Considering that the reaction consists on a cascade 1,4-addition/Michael process we initially worked under the hypothesis that the first step should be considered as the stereodefining step of the overall process. We started by calculating the uncatalyzed background reaction between 1 and 2a. But the energy barrier of the process was found to be 20.0 kcal mol\(^{-1}\). We also considered the participation of the catalyst by forming an encounter complex EC1 with both aldehyde and alcohol without formation of the iminium salt as suggested by Lattanzi, and co-workers for the epoxidation of enones catalyzed by diarylprolinols.\(^{12e}\) After formation of the encounter complex at \(-25.9\) kcal mol\(^{-1}\), the corresponding transition structure was located 3.0 kcal mol\(^{-1}\) below the ground state (for details on these approaches see ESI†).

We next moved to study the reaction between 1 and 2a under covalent activation by pyrrolidine following the well-known combination of iminium and enamine activation manifolds (Scheme 4). We arbitrarily chose the addition of hemiacetal (R)-1 to the Si face of the iminium ion intermediate.\(^{31}\) We also

considered the exclusive participation of the \((E,E)\)-s-trans iminium species in agreement with previous reports.\(^{22}\) Isomeric \((Z,E)\)-iminium salts were also considered but they turned out to be more energetic, as expected (see ESI†). The study was initiated with the formation of encounter complex EC2 (located at \(-22.3\) kcal mol\(^{-1}\) with respect to the reactants) that can be considered as the initial point of a catalytic cycle in which both reactants are activated before the formation of the iminium ion. Evolution of EC2 through TS3 afforded hemiaminal IN1 from which IN2 is formed through TS4 (energy barrier of TS4 2.0 kcal mol\(^{-1}\)) assisted by the hemiacetal reagent 1. IN2 should actually be regarded as a reactive complex formed by the iminium salt, the alcohol and the hydroxyl anion eliminated from the hemiaminal leading to the formation of the C–O bond through the initial conjugate addition. The corresponding transition structure TS5, leading to intermediate enamine ENa, was located at 13.8 kcal mol\(^{-1}\) with respect to EC2 (\(-8.5\) kcal mol\(^{-1}\) with respect to the reactants). Such energy barrier is lower than alternative uncatalyzed TS1 (20 kcal mol\(^{-1}\)) and non-covalent activated TS2 (\(-3.0\) kcal mol\(^{-1}\)), confirming that formation of EC2 is the preferred starting point for the catalytic cycle. It should be taken into consideration that even in achiral series, the addition of two enantiomeric alcohols (R)-1 and (S)-1 by one face of the iminium ion renders two diastereomers. Consequently, this step is determinant for the diastereoselectivity of the reaction involving a kinetic resolution of the two alcohols. We determined during this preliminary analysis that TS5-(R), consisting of the attack of (R)-1 by the Si face of the iminium ion, was the preferred one leading to enamine ENa-(S,S) predicting a relative dr of ca. 4:1 with respect to the addition of (S)-1 leading to ENb-(S,S) (for details see ESI†). Further discussion will be based on this preferred route. Once the initial 1,4-addition reaction has taken place, the second step of the cascade consists in an intramolecular Michael reaction between the enamine and the \(\alpha,\beta\)-unsaturated ketone moiety occurring after migration of the coordinated water (ENa to ENb). The intramolecular Michael reaction on enamine intermediate ENb can take place through the two diastereotopic faces of the pyranone scaffold\(^{22}\) and consequently two transition structures can be found, from which TS6a (located at \(-15.3\) kcal mol\(^{-1}\)) was calculated to be the most stable one. Remarkably, these calculations also indicated that the initial 1,4-addition step (associated to TS5) resulted to be the rate-determining step of the overall reaction (\(\Delta G_{TS5} > \Delta G_{TS6a}\)). Finally, regeneration of activated reactants in EC2 from IN3a should take place through intermediates IN4a and IN5. The energy diagram for the catalytic cycle illustrated in Scheme 4 is given in Fig. 2. From this initial study carried out on this achiral model system it can be concluded that the preferred diastereoselectivity for the reaction will lead to the formation of the final product P1a with a relative 2S*, 3S*, 3aR*, 7aS* configuration. The minor diastereomer (2S*, 3S*, 3aS*, 7aR*) should be formed from the opposite enantiomer of the pronucleophile.

For the analysis of the selectivity of the reaction and prediction of the absolute configuration of the different products formed, the whole real system was considered, involving the participation of chiral catalyst 3a. The study was restricted...
to the key rate-limiting step found for the achiral model system, i.e. the 1,4-addition of hemiacetal 1 to the iminium ion derived from 2a, since the size of the model is in the limit of computational resources. Catalyst 3a is known to operate according to a sterically hindered model<sup>26</sup> in reactions proceeding through both enamine and iminium intermediates, and particularly when these intermediates are involved in Michael-type reactions.<sup>29</sup> As a consequence, only the attack through the less hindered faces of these intermediates (iminium ion or enamine) have been considered in agreement with previous calculations for other reactions.<sup>26</sup> We also considered the (E)-iminium ion (with respect to C≡N bond) as the most reactive isomer according to previous reports by Seebach and co-workers.<sup>34</sup> Therefore and for the complete study, we considered as possible variable structural parameters, the participation of the catalyst through north and south conformations at the pyrrolidine ring, two different diastereoisomers (Z and E) of the C≡C bond of the iminium ion intermediate (resulting into the reaction with the Michael donor 1 through a different facial selectivity) and the participation of the two enantiomeric hemiacetal reagents 1 (in order to evaluate kinetic resolution). Thus, a total of 8 TS were located and characterized (see ESI† for details). Boltzmann analysis for these transition structures predicted a 91 : 9 ratio of products 4 : 5, in good agreement with experimental observations (considering that product 4 subsequently epimerizes onto 6, see below). The two preferred transition structures TS<sup>5-r1</sup> and TS<sup>5-r2</sup> leading to 5 and 4, respectively, are shown in Fig. 3 (for geometries see ESI†).

The difference in energy of 1.6 kcal mol<sup>−1</sup> observed between TS<sup>5-r1</sup> and TS<sup>5-r2</sup> can be explained on the basis of a combination of electronic effects and steric interactions. In fact, 1,4-addition is facilitated by the loss of the proton of the OH group of the hemiacetal to form a water molecule upon combination with the hydroxyl anion. NCI analysis (see ESI†) shows that, in the transition state, the negative charge is located between the water oxygen atom and the attacking oxygen of 1 (actually, most of the negative charge is located at the oxygen atom of 1 which should be interpreted as the driving force for the nucleophilic attack). The partial negative charge located at the incipient water molecule should be close to the iminium nitrogen atom which has a partial positive charge. This electrostatic interaction forces the orientation of the attack of the hydroxyl group, which should release the proton to form water. According to this model calculations predict a kinetic resolution in favour of the attack of (R)-1 to give compound 4 (which might epimerize, see below) as the major isomer.

The mechanistic picture presented up to this moment involves the occurrence of a DKR process through the fast racemization of the starting hemiacetal reagent 1 before it gets involved in the cascade 1,4-addition/Michael reaction.<sup>37</sup> However, a potential DYKAT cannot be discarded as the epimerization of the 7a position could also take place after the 1,4-addition process (through the potential formation of a dienol intermediate under the intermediacy of the Brønsted acid co-catalyst 7, see DYKAT intermediates I and II in Scheme 5). In order to rule out this possibility, the resolution process of the starting hydroxypyranone 1 was studied experimentally. For this purpose, we carried out the reaction between cinnamaldehyde (2a) and deuterated hydroxypyranone 1 under optimized conditions, observing the formation of products 5a<sup>−2</sup>H and 6a<sup>−2</sup>H in good yield and with an excellent enantiocontrol (Scheme 6).

The fact that the deuterium atom present at the starting material had been preserved in the same position across the

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**Fig. 2** Energy diagram of the catalytic cycle illustrated in Scheme 4.

**Fig. 3** TS structures leading to compounds 4 and 5.

**Scheme 5** Possible intermediates involved in the kinetic resolution process.
overall cascade reaction confirmed our initial hypothesis that a DKR process was operating and that the possible intermediates that could operate through a hypothetical DYKAT process (DYKAT intermediates I and II) were not formed in the reaction. The racemization of the starting material could eventually occur through the participation of dienol intermediate III, through oxidopyrylium ylide IV or, alternatively, via ring-opening of the hemiacetal moiety through intermediate V. The experiment using deuterated substrate 1 shown in Scheme 6 directly rules out the possible participation of intermediate III, but it does not provide any evidence to support the participation of either IV or V. In order to discern between IV and V as the intermediates involved in the racemization process we carried out another computational study through the several channels involving those intermediates and under the intermediacy of the Brønsted acid. For that purpose, this process was initially modelled by using formic acid as promoter of the reaction.

From the several paths studied (see ESI† for details) there is a clear preference for the open-chain intermediate V which is located at 3.5 kcal mol\(^{-1}\) with respect to compound 1. Intermediate IV is located at 20 kcal mol\(^{-1}\). The corresponding barriers leading to V and IV were found to be 11.9 and 21.3 kcal mol\(^{-1}\), respectively. We also calculated a more realistic transition structure leading to intermediate V promoted by either water or thiourea 7 for which energy barriers of 21.1 and 28.8 kcal mol\(^{-1}\) were found (see ESI†). Consequently, this computational study shows that the calculated barrier for the racemization of 1 is 11.9 kcal mol\(^{-1}\), which is lower than the following rate-determining step (13.8 kcal mol\(^{-1}\)) associated to the oxa-Michael/Michael cascade sequence, thus being consistent with a DKR process. The proposed racemization of 1 through an open-chain intermediate is in good agreement with highly accurate recent studies on mutarotation of D-glucose in water as a solvent.\(^{18}\)

Taking into account all experimental and computational investigations, we propose a catalytic cycle (Scheme 7) based on the known iminium/enamine activation manifold starting with the conjugate addition of the hemiacetal moiety of pyranone 1 with the intermediate iminium ion that installs the first stereo-center and in which one of the enantiomers of 1 is reacting faster than the other. This type of 1,4-additions of O-nucleophiles with enals under iminium activation has been proposed to be reversible processes,\(^{19}\) which means that in our case it must be followed by a fast intramolecular Michael reaction that generates the other two stereocenters. Once the product has been released and catalyst regenerated, preferential formation of diastereoisomer 4 should occur. Finally, calculations predict the formation of isomer 4 (2S, 3S, 3aR, 7aS) as the major one, and compound 5 (2S, 3S, 3aS, 7aR) as the minor one. However, when β-aryl substituted enals were employed as substrates mixtures of 5 and 6 were experimentally obtained, the latter having a (2S, 3R, 3aS, 7aR) configuration, and being this isomer obtained almost exclusively after \textit{in situ} acidic treatment (see Table 2). This behaviour, together with the data obtained by calculations suggests that, once isomer 4 is formed, it undergoes fast epimerization at the α-position to the formyl substituent. Experimentally, epimerization of 4 into 6 has been observed under acidic conditions for those substrates containing aryl substituents (R = Ph). On the other hand, for adducts incorporating alkyl substituents at that position (R = Et), epimerization was observed in rather less extent after treatment with hydrochloric acid, and no epimerization at all was detected.
when the reaction was carried out in the presence of trichloroacetic acid.\(^\text{40}\)

In order to understand this atypical behaviour, an exhaustive conformational analysis showed that epimerization of 4 into 6 is thermodynamically favoured independently of the nature (aromatic vs. aliphatic) of the substituent. This 4 to 6 epimerization process was subsequently studied in detail using DFT calculations in order to determine the energy barrier and to analyze the kinetics of the process (see ESI†). The preferred pathway corresponds to the formation of \((E)\)-enols and energy barriers showed that epimerization of adducts containing an aryl substituent \((R = \text{Ph})\) is favoured by 1.5 kcal mol\(^{-1}\) with respect to those containing an alkyl group at the same position \((R = \text{Et})\). Accordingly, epimerization of 4a is kinetically favoured and it should be expected that epimerization of 4a to 6a takes place faster than that of 4j to 6j.

A complete epimerization could not be achieved in the reaction of aliphatic enals because they tend to decompose under treatment with aqueous HCl. Indeed, by using 1 M HCl \((pK_a < 1)\) a slower epimerization was observed for 4j (see Table 2, entry 9) with respect to 4a, which epimerized completely. Other acids like benzoic acid \((pK_a = 4.19)\) and trichloroacetic acid \((pK_a = 0.77)\) were not acidic enough to promote epimerization at an appreciable rate. In fact, modelization using formic acid \((pK_a = 3.75)\) provided energy barriers of \(ca. 22 \text{ kcal mol}^{-1}\) which are in the limit for a spontaneous process at room temperature (see ESI†).\(^{41}\)

### Conclusions

The enantio- and diastereoselective synthesis of furopyranes has been developed through a transformation that operates under a dynamic kinetic resolution process of involving a hemiacetal reagent as unconventional oxygen-centered Michael donor that undergoes oxa-Michael/Michael cascade reaction with enals in the presence of a chiral secondary amine catalyst. This transformation constitutes a rare example of cascade iminium/enamine reaction with an unconventional oxygen pronucleophile that involves the stereocontrolled formation of one single enantiomer over 16 possible stereoisomers. Experimental studies together with computational methods demonstrate that the initial racemization of the hemiacetal occurs through an open-chain pathway before the catalytic cycle takes place. A final epimerization in the stereocenter incorporating the formyl group also takes place when the thermodynamically more stable compound can be isolated without decomposition.

### Acknowledgements

This research was supported by the Spanish MINECO (FEDER-CTQ2014-52107-P, FEDER-CTQ2013-44367-C2-1-P and FEDER-CTQ2016-76155-R), the Basque Government (Grupos IT908-16), UPV/EHU (IFI QOSYC 11/22) and Government of Aragón (Grupos Consolidados, E.10). D. R.-L. thanks MEC for a predoctoral FPU fellowship. The authors thankfully acknowledge the resources from the supercomputers “Memento” and “Cierzo”, technical expertise and assistance provided by BIFI-ZCAM (Universidad de Zaragoza, Spain).

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2 s

42 of 53 seconds.}