Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of in situ Generatedortho-Quinone Methides

Youwei Xie, and Benjamin List*

Abstract: Here we describe the first catalytic asymmetric intramolecular [4+2] cycloaddition of in situ generated ortho-quinone methides. Catalyzed by a confined chiral imidodiphosphoric acid, various salicylaldehydes react with dienyl alcohols to give transient ortho-quinone methide intermediates, which undergo an intramolecular [4+2] cycloaddition to provide highly functionalized furanochromanes and pyranochromanes in excellent diastereoselectivity and enantioselectivity.

o-Quinone methides (o-QMs) have been well-studied and applied in a variety of transformations during the last few decades.[1] They are also the key intermediates in a number of biomimetic natural product syntheses, typically engaging in [4+2] hetero-Diels–Alder reactions.[1a,2] Several approaches have been developed towards in situ generation of these highly reactive intermediates,[13-15] and their application in catalytic asymmetric transformations[16]However, there are only few reports on catalytic asymmetric [4+2] cycloadditions of o-QMs,[11] and an intramolecular variant is, to the best of our knowledge, completely unknown. The development of such a transformation occurred to be desirable to us as it would allow direct access to various tricyclic frameworks with a chromane moiety, a structural motif frequently seen in natural products (Figure 1). Here, we show that by utilizing a confined Brensted acid catalyst,[12] this transformation can indeed be accomplished highly stereoselectively.

The challenges of applying o-QMs in asymmetric [4+2] cycloadditions are not only associated with their transient nature, but also with their weak and ill-defined interactions with enantiopure catalysts. Existing methods rely on either simultaneously activating both the o-QM and its reaction partner,[11] or on the exclusive activation of o-QMs towards cycloadditions with styrenes.[11b]

Non-asymmetric intramolecular [4+2] cycloadditions have previously been developed and suggested to proceed via protonated o-QMs.[1b-1d] We hypothesized that the confined chiral pocket of the imidodiphosphoric acid catalysts[12] could provide sufficient activation and enantiodifferentiation for this reaction. Indeed, upon treating salicylaldehyde (1a) with dienyl alcohol 2a in the presence of TRIP (4a), product 3a was isolated in poor yield and moderate selectivity (Scheme 1).

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However, significantly improved yield and selectivity could be achieved by using imidodiphosphoric acid catalyst 4b, which catalyzed the reaction efficiently to give 3a as the only isolable product in 81% NMR yield with an excellent enantiomeric ratio of 97:3. The enantiomeric ratio could be further increased to 99:1 by using cyclohexane as a solvent (see Supporting Information for more details of catalyst and reaction condition optimization). The application of a dienyl alcohol such as 2a was crucial for high reactivity and selectivity, and switching to other homoallylic alcohols with isolated alkene moieties led to significantly reduced reactivity and selectivity (Table S6).

Table 1. [4 + 2] Cycloaddition of different salicylaldehyde derivatives.[a]

<table>
<thead>
<tr>
<th>R</th>
<th>4b (5 mol%)</th>
<th>cyclohexane</th>
<th>MS (5 Å), r.t.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>MeO</td>
<td>EtO</td>
</tr>
<tr>
<td>3a</td>
<td>2 d, 84%, 99:1 e.r.</td>
<td>16 h, 83%, 98:2 e.r.</td>
<td>1 d, 86%, 98:5:1.5 e.r.</td>
</tr>
<tr>
<td>3b</td>
<td>3 d, 84%, 98:5:1.5 e.r.</td>
<td>2 d, 80%, 98:2 e.r.</td>
<td>6 d, 84%, 96:4 e.r.</td>
</tr>
<tr>
<td>3c</td>
<td>6 d, 84%, 96:4 e.r.</td>
<td>3 g, 91%, 99:1 e.r.</td>
<td>2 d, 80%, 99:1 e.r.</td>
</tr>
<tr>
<td>3d</td>
<td>24 h, 81%, 98:5:1.5 e.r.</td>
<td>4 d, 80%, 99:1 e.r.</td>
<td>3 d, 82%, 98:2 e.r.</td>
</tr>
<tr>
<td>3f</td>
<td>24 h, 81%, 98:5:1.5 e.r.</td>
<td>4 d, 80%, 99:1 e.r.</td>
<td>3 d, 82%, 98:2 e.r.</td>
</tr>
<tr>
<td>3i</td>
<td>3 d, 88%, 98:5:1.5 e.r.</td>
<td>2 d, 81%, 92:8 e.r.</td>
<td>3 d, trace</td>
</tr>
</tbody>
</table>

[a] Reactions were performed using catalyst 4b (5 mol%), 1.05 equiv. of aldehyde 1, 1.0 equiv. of diene 2a and 5 Å molecular sieves (0.3 g/mmol) in cyclohexane (0.1 M), at r.t. for the indicated period of time, isolated yields, d.r. > 20:1 for all substrates shown.

With the optimized reaction condition in hand, we next explored the scope of this reaction (Table 1). A variety of commercially available salicylaldehyde derivatives were tested using 5 mol% of catalyst 4b. Electron-neutral (1a, 1d), electron-rich (1b), electron-poor (1c) and sterically bulky substituent (1g) were all tolerated at the 5-position of the aromatic ring, and the corresponding products were obtained in good yields with excellent diastereo- and enantioselectivity. Substituents at the 3- and 4-positions (1e, 1f, 1m) are well tolerated as well. Halogenated (3h–3j) and dihalogenated (3k, 3l) products could also be obtained in good yields and excellent selectivity, suggesting further functionalizations of the aromatic ring to be possible. Only a substrate with substitution at the 6-position did not provide the corresponding product in detectable amount (3n). The absolute configuration of product 3h was unambiguously assigned by single-crystal X-ray analysis while that of the others was assigned by analogy (Table 1 and Figure S1).[19] Temperature (see the Supporting Information).

We also explored several dienyl alcohols with different substitution patterns (Table 2). Substrates with less substitution (2b), longer alkyl chain substituents (2c, 2d), or an aromatic substituent (2e) were all well tolerated. When the distant alkene was part of a ring (2f), tetracyclic product 5f could be obtained in good yield and excellent selectivity. The distant alkene could also be replaced by a phenyl group (2g), and the corresponding product 5g was obtained in excellent selectivity. Furthermore, this method was equally efficient in the synthesis of a pyranochromane, and product 5h was isolated as the only product in good yield and excellent selectivity when the homolog of 2a, 2h was used. A dienyl alcohol with a terminal alkene was not suitable as substrate since the corresponding product was formed at extremely low reaction rate, even at elevated temperature (see the Supporting Information).

Table 2. [4 + 2] Cycloaddition of different dienyl alcohol derivatives.[a]

<table>
<thead>
<tr>
<th>R</th>
<th>4b (5 mol%)</th>
<th>cyclohexane</th>
<th>MS (5 Å), r.t.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>2 d, 78%, 98:2 e.r.</td>
<td>3 d, 81%, 98:2 e.r.</td>
<td>3 d, 82%, 97:5:2.5 e.r.</td>
</tr>
<tr>
<td>5c</td>
<td>3 d, 82%, 97:5:2.5 e.r.</td>
<td>5 d, 83%, 98:5:1.5 e.r.</td>
<td></td>
</tr>
<tr>
<td>5e</td>
<td>4 d, 87%, 99:1 e.r.</td>
<td>5 f, 83%, 99:1 e.r.</td>
<td></td>
</tr>
<tr>
<td>5f</td>
<td>5 h, 83%, 98:5:1.5 e.r.</td>
<td>5 i, 93%, 99:1 e.r.</td>
<td></td>
</tr>
<tr>
<td>5g</td>
<td>10 d, 84%, &gt;99:1 e.r.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reactions were performed using catalyst 4b (5 mol%), 1.05 equivalent of 1a, 1.0 equivalent of 2 and 5 Å molecular sieves (0.3 g/mmol) in cyclohexane (0.1 M), at room temperature for the indicated period of time, isolated yields, d.r. > 20:1 for all substrates shown. [b] The starting dienyl alcohol was enantiomerically pure and the absolute configuration is indicated in the product.
substrates depending on the absolute configuration of the chiral dienyl alcohol starting material. In the matched case, the corresponding product was formed in excellent diastereoselectivity (5i, 5j in table 2), while in the mismatched case, the corresponding product was obtained with moderate diastereoselectivity (5i', 5j' in table S7). In both cases, no erosion of enantiopurity was observed, and the products were observed with the same level of enantiopurity as their starting alcohols. When an achiral catalyst was used, a complex mixture of four to eight diastereomers was obtained, again supporting the excellent control enabled by confined acid catalyst 4b in activating o-QMs for stereoselective transformations (see table S7 in the Supporting Information).

Encouraged by these results we next explored the possibility of developing a diastereoselective and enantioselective synthesis of furanochromanes from racemic chiral dienyl alcohols via kinetic resolution (KR). Indeed, as shown in Scheme 2, chiral alcohols (rac)-2i or (rac)-2j were exposed to the reaction condition and after approximately 50% conversion, products 5i or 5j were obtained in good yield with excellent enantioselectivity and moderate to good diastereoselectivity. The minor diastereomers 5i' and 5j' were also obtained with excellent enantioselectivity.

To gain more information on the reaction mechanism, we reacted aldehyde 1a with homoallylic alcohol cis-2g. While trans-2g gave the corresponding trans-product 5g in excellent diastereo- and enantioselectivity (Table 2), cis-2g gave a mixture of cis-products 5g' and 5g'' in moderate enantioselectivity (Scheme 4). Accordingly the stereochemical relationship of the C-C double bond was stereospecifically transferred into product in both cases (see scheme S1 in the Supporting Information). This result is consistent with the suggested concerted path a, even though stepwise path b cannot be entirely ruled out at this point.

In summary, we have developed the first catalytic asymmetric intramolecular [4+2] cycloadditions of o-QMs. Our method allows fast access to a variety of highly functionalized furanochromane and pyranochromane derivatives. Diastereo- and enantioselectivity observed in this reaction is a result of the activation of ortho-quinone methide intermediate in the confined chiral pocket of IDP catalyst 4b. Even compared to the previously developed non-asymmetric variants, our method has a very broad substrate scope and the resulting products are functionalized for further elaboration. We envisage that this method can be applied in the asymmetric synthesis of a variety of useful natural products. Research along these lines is currently going on in our laboratory and will be reported in due course.

Keywords: hetero-Diels–Alder reaction • [4+2] cycloaddition • ortho-quinone methide • organocatalysis • confined Brensted acid
