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Migratory Dynamic Kinetic Resolution of Carbocyclic Allylic Alcohols

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Supporting Information Placeholder

ABSTRACT: A novel migratory dynamic kinetic resolution based on the interplay between an enzyme acylation catalyst and a heterogeneous Brønsted acid as isomerization/racemization catalyst gives rise to carbocyclic allylic esters with excellent stereoselectivity from readily available tertiary carbinols. An easy-to-use teabag setup combining resin-bound catalysts, a biphasic isooctane-water solvent system and a highly lipophilic acyl donor efficiently suppresses side reactions and allows for the preparation of functionalized carbocyclic building blocks in high yields and optical purity.

The use of lipases as inexpensive and reliable biocatalysts in kinetic resolutions and desymmetrization reactions for the preparation of enantiomerically enriched alcohols has evolved into a fundamental and well accepted approach within the synthetic-organic community.1 Both primary and secondary hydroxy-functionalized compounds or their corresponding ester derivatives can be engaged in enantiodiscriminating transformations giving rise to optically active products in excellent optical purities.2 Tertiary alcohols, on the other hand, proved to be much more problematic as the majority of hydrolases lack both activity and selectivity for these kinds of structural entities.3 However, some exceptions to this rule have been reported for tertiary propargylic carbinols with a few serine hydrolases, where the enzyme was able to productively accommodate the substrates’ terminal alkyne moiety.4 As part of our studies toward the total synthesis of taylofuran A, we pursued investigations employing 1a as starting material en route to the sesquiterpene natural product.5 With an ethynyl substituent at the tertiary carbinol, we envisioned a lipase-catalyzed hydrolytic kinetic resolution of the corresponding acetate as entry to an enantioselective path. To our surprise, Candida antarctica lipase B (CALB) yielded a highly enantiomerically enriched carbinol product beyond selectivities previously described for these substrate structures. Unfortunately, spectroscopic analysis disclosed formation of a secondary alcohol product (2a) rather than the desired 1a (Scheme 1, top). The formation of 2a could be traced back to a 1,3-transposition during the preceding, mildly acidic, acetylation step in acetic anhydride/pyridine. Acid-catalyzed isomerizations of allylic alcohols have recently been reported by Mulzer and coworkers using trifluoroacetic acid,6 but obviously this isomerization is also promoted by weaker acids. Our finding that less acidic conditions can

Scheme 1. Inherent lability of tertiary allylic carbinols: synthetic limitation or opportunity?

Undesired isomerization during the attempted resolution of 1a

\[
\begin{align*}
\text{rac-1a} & \quad \text{1) AcO, Py} \\
& \quad \text{2) lipase \text{aq buffer}} \\
& \quad \begin{array}{c}
\text{OH} \\
\text{CH}_3
\end{array} \\
& \quad + \\
& \begin{array}{c}
\text{OH} \\
\text{CH}_3
\end{array}
\end{align*}
\]

(rac)-OH

(rac)-2a (97%, ee = 99%)

as basis for the development of a migratory dynamic kinetic resolution?

\[
\begin{align*}
\text{rac-1a} & \quad \text{acid catalyst} + \text{lipase catalyst} \\
& \quad \text{acetyl donor} \\
& \quad \begin{array}{c}
\text{OH} \\
\text{CH}_3
\end{array} \\
& \quad + \\
& \begin{array}{c}
\text{OH} \\
\text{CH}_3
\end{array}
\end{align*}
\]

(rac)-OH

(rac)-3a (97%, ee = 99%)

be used brought us to reflect upon a way to exploit this reactivity in a more productive fashion. The inherent lability of these allylic alcohols should make them attractive targets for stereoselective transformations taking advantage of this kind of dynamic behavior (Scheme 1, bottom).7,8 The preparation of cyclic tertiary allylic carbinols is often a very easy task (addition of C-nucleophiles to enones) while the synthesis of their secondary isomers involves in most cases multi-step procedures. Hence, from a synthetic point of view, the development of a catalytic process combining the isomerization of tertiary to secondary allylic alcohols with a subsequent dynamic kinetic resolution based on the interplay between an acid-catalyzed racemization and a lipase-mediated enantiodiscriminating acetylation appeared to be a worthwhile challenge, providing a rapid access to

"
optically enriched, synthetically valuable allylic carbinol derivatives.

The 1,3-transposition and the racemization of the secondary alcohol both rely on the acid-catalyzed formation of transient allylic cationic intermediates. Thus, on the basis of the model substrates 1b and 2b, the efficiency of the 1,3-transposition from carbinal 1 to the racemic secondary alcohol 2 as well as the racemization of enantioenriched 2 (ee = 99%) was investigated employing different acidic ion-exchange resins. Pentane was initially chosen as the reaction medium, due to its compatibility with the lipase-catalyzed acylation reaction, later to be added. To our delight, carboxylic acid-loaded Amberlite 120 was active in the isomerization of 1b (Table 1, entry 1) as well as in the racemization of (S)-2b (Table 1, entry 2), however, analysis of the reaction mixture after 5 hours revealed substantial contamination with several side products with ether 4b as the major constituent. Similar results were obtained using the sulfonic acid-bearings resins Amberlyst 15 and Dowex 50Wx4, respectively. Both showed good activity in the isomerization reactions but likewise suffered from pronounced ether formation (Table 1, entries 3 – 6). Providing water as nucleophile to quickly trap potential cationic species and thus avoid dehydration product 4b, a two-phase system based on isooctane and water as non-miscible liquid layers was tested. In this setting, isomerization to the secondary alcohol 2b by Amberlyst 15 proceeded with reasonable rates detecting only a few percent of the ethereal side product (Table 1, entry 7). With enantiopure (S)-2b as starting material, almost complete racemization was achieved after 5 hours and as opposed to the purely organic solvent system perfect recovery of the secondary alcohol was accomplished (Table 1, entry 8). Also Dowex 50Wx4 proved to be a suitable catalyst under the biphasic reaction conditions and while rates of racemization were slightly reduced, the absence of any detectable 4b in either 1,3-transposition or racemization prompted us to continue the method development with this acid resin (Table 1, entries 9–10).

The necessity of an aqueous cosolvent in the optimal transposition/racemization system raised concerns about the interference with the desired biocatalytic esterification as in the presence of water lipases can catalyze the reverse reaction, that is, ester hydrolysis. As described by Jacobs and coworkers in their work on the zeolite/lipase-catalyzed DKR of arylenolhs, this problem can be solved for instance by fixation of the enzyme in a rotating steel basket inside the reaction vessel. However, we imagined that a simple nylon fabric might serve as a practical alternative to the steel basket. Once filled with the bead of the immobilized enzyme, the nylon basket could be immersed into the organic top layer like a catalytic teabag (Figure 1). Standard fine-woven nylon mesh from the local department store (available by the meter) proved to be a well-suited and cheap material for this purpose that combined perfect immobilization of the acrylic beads of Novozym 435 (CALB) with high flexibility to adjust reaction scale and enzyme loading without being limited to a certain size of a reaction vessel's components.

The success of the envisaged migratory dynamic kinetic resolution should apparently be strongly dependent on the efficacy of separating the individual reaction steps. With increased water solubility of the reaction components both undesired background decomposition of the vinyl carboxylate as well as acid-mediated (de-)esterification ought to become significant factors. Hence, lipophilicity of the acyl donor and consequently lipophilicity of the resulting ester product proved to be a key parameter in this regard. In a simple kinetic resolution of rac-2b by CALB in anhydrous isooctane the chain length of the donor had only marginal influence on the selectivity with relative rates ($k_{1b}/k_{1S}$)

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**Table 1.** Screening catalyst abilities for the selective transposition and racemization 6

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>acid resin</th>
<th>solvent</th>
<th>2b (%)</th>
<th>ee 2b (%)</th>
<th>4b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rac-1b</td>
<td>Amberlite 120</td>
<td>pentane</td>
<td>31</td>
<td>–</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>(S)-2b</td>
<td>Amberlite 120</td>
<td>pentane</td>
<td>24</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>rac-1b</td>
<td>Amberlyst 15</td>
<td>pentane</td>
<td>39</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>(S)-2b</td>
<td>Amberlyst 15</td>
<td>pentane</td>
<td>9</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>rac-1b</td>
<td>Dowex 50Wx4</td>
<td>pentane</td>
<td>26</td>
<td>–</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>(S)-2b</td>
<td>Dowex 50Wx4</td>
<td>pentane</td>
<td>21</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>rac-1b</td>
<td>Amberlyst 15</td>
<td>isooctane/H2O</td>
<td>68</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>(S)-2b</td>
<td>Amberlyst 15</td>
<td>isooctane/H2O</td>
<td>99</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>rac-1b</td>
<td>Dowex 50Wx4</td>
<td>isooctane/H2O</td>
<td>74</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>(S)-2b</td>
<td>Dowex 50Wx4</td>
<td>isooctane/H2O</td>
<td>99</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: rac-1b (10 mg) or (S)-2b (10 mg, ee = 99%), ion-exchange resin (10 mg) in 4 mL pentane or isooctane/water (1:1) at room temperature. Product ratios were determined by 1H-NMR, enantiomeric excesses were determined by chiral HPLC.

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![Figure 1. Schematic drawing and practical implementation of the teabag approach](image-url)
greater than 200 in all cases. However, initial attempts to combine the Dowex-catalyzed isomerizations with a lipase-mediated acylation employing the teabag setup revealed a strong dependence of the products’ optical purity from the nature of the vinyl ester. While the use of partially water-miscible vinyl acetate (log $P = 0.7$) led to acetyl ester 3b in only moderate enantiomeric excess of 81%, more lipophilic donors such as vinyl butyrate (log $P = 1.6$) and in particular vinyl caprate (log $P = 4.6$) helped to overcome this shortcoming and the latter one allowed for an efficient dynamic kinetic resolution with good yield and excellent enantiopurity of the caprate ($R$)-6b (ee = 99%). Estimation of the partition coefficients of the carbocyclic reaction constituents further underlined the beneficial effect of long-chain donors in this system by efficiently raising affinity of the reaction products for the non-aqueous layer as a safe haven (log $P_{i}$ = 2.6; log $P_{u}$ = 3.3; log $P_{i2}$ = 6.0).13

In order to survey the general applicability of this method, a series of tertiary carbinols was synthesized by addition of organolithium or organomagnesium nucleophiles (RLi, or RMgX, see Supporting Information for experimental details) to the corresponding enones. The racemic allylic alcohols 1a–i thus obtained were subsequently subjected to an acid/lipase-catalyzed migratory dynamic kinetic resolution (Scheme 3). Our originally tested carbinol 1a proved to be substantially more sensitive to the acid catalyst than cyclohexenol 1b and extensive substrate decomposition was observed under standard conditions. By reduction of the Dowex loading by a factor of ten, however, an efficient DKR was obtained and the enantiopure conjugated enyne 6a was isolated in 82% yield. As for 1a also cyclopentenol 1c required a lower acid content to suppress side reactions. After these marginal adjustments, 6c could be isolated in high yield and decent enantioselectivity.14 By contrast, the one-carbon ring expanded cycloheptenol 1d isomerized much slower than 1b and extended reaction times were required to achieve acceptable conversion. Nonetheless, after four to five days not only cycloheptenyl caprate 6d but also various cyclohexenyl derivatives carrying substituted aryl moieties (6e – 6g) were obtained in good to excellent yields and optical purities beyond 99%.

For the alkyl-substituted substrate 1h the migratory DKR gave a low yield due to a very slow isomerization to the secondary alcohol 2h. Finally, as exemplified for styrene 6i the teabag protocol is also well applicable for acyclic allylic carbinols and migratory DKR led to ($R$)-6i in 82% yield and 99% enantiomeric excess.

### Scheme 3. Scope of the migratory dynamic kinetic resolution

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Optical Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>6a</td>
<td>(&gt;98%)</td>
</tr>
<tr>
<td>1b</td>
<td>6b</td>
<td>99%</td>
</tr>
<tr>
<td>1c</td>
<td>6c</td>
<td>85%</td>
</tr>
<tr>
<td>1d</td>
<td>6d</td>
<td>90%</td>
</tr>
<tr>
<td>1e</td>
<td>6e</td>
<td>74%</td>
</tr>
<tr>
<td>1f</td>
<td>6f</td>
<td>74%</td>
</tr>
<tr>
<td>1g</td>
<td>6g</td>
<td>81%</td>
</tr>
<tr>
<td>1h</td>
<td>6h</td>
<td>81%</td>
</tr>
<tr>
<td>1i</td>
<td>6i</td>
<td>81%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: rac-1 (0.5 mmol), vinyl caprate (2.5 mmol), Dowex 50Wx4 (100 wt %), lipase (100 wt %), isooctane (20 mL), water (20 mL), room temperature, 300 rpm. Isolated yields after flash chromatography, optical purity determined by chiral HPLC. Capr = caprate. [b] Reduced Dowex loading (10 wt %) in case of 1a and 1e.

The simple product isolation from the two-phase system in combination with the easy recovery of the two heterogeneous catalysts prompted us to perform recycling studies on this dynamic resolution system. It was possible to reuse both Dowex 50Wx4 and CALB for more than six rounds of cataysis in the migratory DKR of substrate 1b without substantial loss of reactivity or selectivity. Here, at the end of each reaction cycle the organic layer was removed and the product ($R$)-6b was extracted from the aqueous layer containing the heterogeneous acid. A new batch of substrate and acyl donor in isooctane was added on top of the water layer and the lipase-containing teabag was re-immersed into the organic layer. Throughout the recyclability study, the conversion rates were close to identical within the margins of error with final conversions after 22 h between 80% and 90% in all runs. In all cases, perfect optical purity of the caprate 6b (ee > 99%) was achieved.
In summary, exploiting the lability of tertiary allylic alcohols under mildly acidic conditions, a preparatively convenient protocol for the synthesis of enantiopure secondary carbocyclic esters was developed based on a migratory dynamic kinetic resolution mechanism. Featuring resin-bound acidic catalyst in combination with immobilized lipases kept in a handy teabag-like immobilization system, this chemoenzymatic strategy represents an easy-to-use and straightforward approach toward synthetically valuable carbocyclic building blocks.

ASSOCIATED CONTENT

Supporting Information
Full experimental details for the preparation of the compounds, characterization data sets and copies of $^1$H- and $^{13}$C-NMR are provided. This material is available free of charge via the internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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REFERENCES


(14) Lipase from Pseudomonas cepacia (Amano PS-D I, diatomite as support) was used for this substrate due to a substantially higher enantioselectivity ($E_{calcd}= 1.8$, $E_{exp} = 13.1$, in the acylative kinetic resolution of alcohol 2c using vinyl acetate). However, to achieve very high optical purity of 6c, an in-depth enzyme screening would be necessary.

Figure 2. Recyclability of the resin-bound catalysts in the migratory dynamic kinetic resolution of alcohol rac-1b.