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Migratory Dynamic Kinetic Resolution of Carbocyclic Allylic Alcohols

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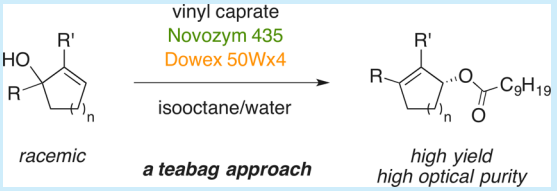
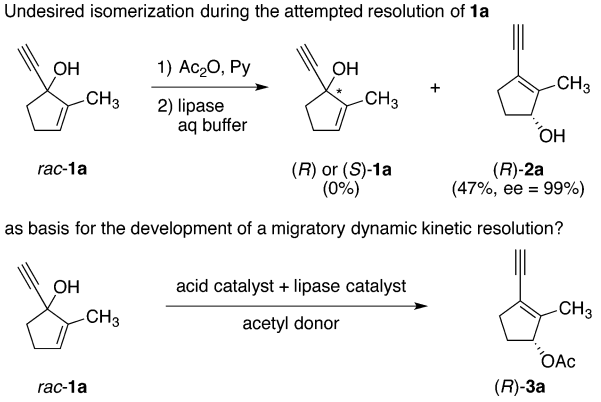
Supporting Information

ABSTRACT: A novel migratory dynamic kinetic resolution based on the interplay between an enzyme acylation catalyst and a heterogeneous Brønsted acid as an 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 enantioenriched 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 co-workers using trifluoroacetic acid,[6] but obviously this isomerization is also promoted by weaker acids. Our finding that less acidic conditions can 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 multistep 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 acylation appeared to be a worthwhile challenge, providing a rapid access to optically enriched, synthetically valuable allylic carbinol derivatives.

Scheme 1. Inherent Lability of Tertiary Allylic Carbinols: Synthetic Limitation or Opportunity?



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 carbinol **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.

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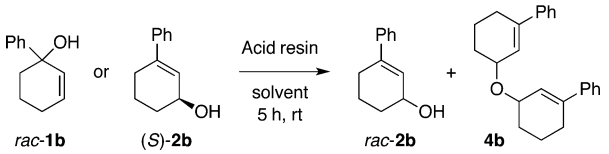
Pentane was initially chosen as the reaction medium, due to its compatibility with the lipase-catalyzed acylation reaction, later to be added. To our delight, carboxylic acid loaded Amberlite 120 was active in the isomerization of **1b** (Table 1, entry 1) as

Table 1. Screening Catalyst Abilities for the Selective Transposition and Racemization[a]



rac-**1b** (*S*)-**2b** *rac*-**2b** **4b**

entry	alcohol	acid resin	solvent	**2b** (%)	ee **2b** (%)	**4b** (%)
1	*rac*-**1b**	Amberlite 120	pentane	31	–	34
2	(*S*)-**2b**	Amberlite 120	pentane	24	31	36
3	*rac*-**1b**	Amberlyst 15	pentane	39	–	26
4	(*S*)-**2b**	Amberlyst 15	pentane	9	5	35
5	*rac*-**1b**	Dowex 50Wx4	pentane	26	–	31
6	(*S*)-**2b**	Dowex 50Wx4	pentane	21	25	36
7	*rac*-**1b**	Amberlyst 15	isooctane/ H_2O	68	–	5
8	(*S*)-**2b**	Amberlyst 15	isooctane/ H_2O	99	5	0
9	*rac*-**1b**	Dowex 50Wx4	isooctane/ H_2O	74	–	0
10	(*S*)-**2b**	Dowex 50Wx4	isooctane/ H_2O	99	22	0

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

well as in the racemization of (*S*)-**2b** (Table 1, entry 2); however, analysis of the reaction mixture after 5 h revealed substantial contamination with several side products with ether **4b** as the major constituent. Similar results were obtained using the sulfonic acid bearing 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 the nucleophile to quickly trap potential cationic species and thus avoid dehydration product **4b**, a two-phase system based on isooctane and water as nonmiscible liquid layers was tested.[10] In this setting, isomerization to the secondary alcohol **2b** by Amberlyst 15 proceeded with reasonable rates detecting only a few percent of the Etheral side product (Table 1, entry 7). With enantiopure (*S*)-**2b** as starting material, almost complete racemization was achieved after 5 h 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 co-workers in their work on the zeolite/lipase-catalyzed dynamic kinetic resolution (DKR) of arylethanols,[10] this problem can be solved for instance by fixation of the enzyme in a rotating steel basket inside the reaction vessel.[11] 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).[12] Standard fine-

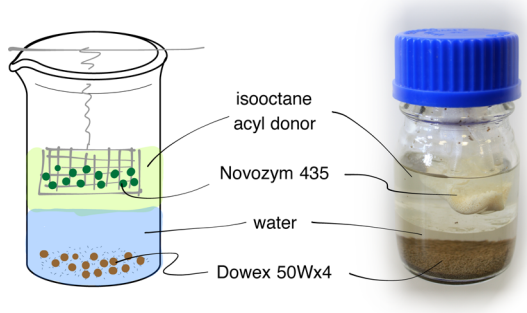


Figure 1. Schematic drawing and practical implementation of the teabag approach.

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 ($k_{(R)}/k_{(S)}$) 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 a 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%) (Scheme 2). 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 the affinity of the reaction products for the nonaqueous layer as a safe haven (log $P_{(2b)}$ = 2.6; log $P_{(4b)}$ = 3.3; log $P_{(6b)}$ > 6.0).[13]

In order to survey the general applicability of this method, a series of tertiary carbinols were synthesized by addition of

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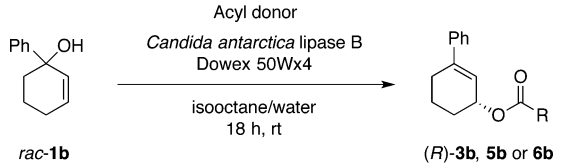
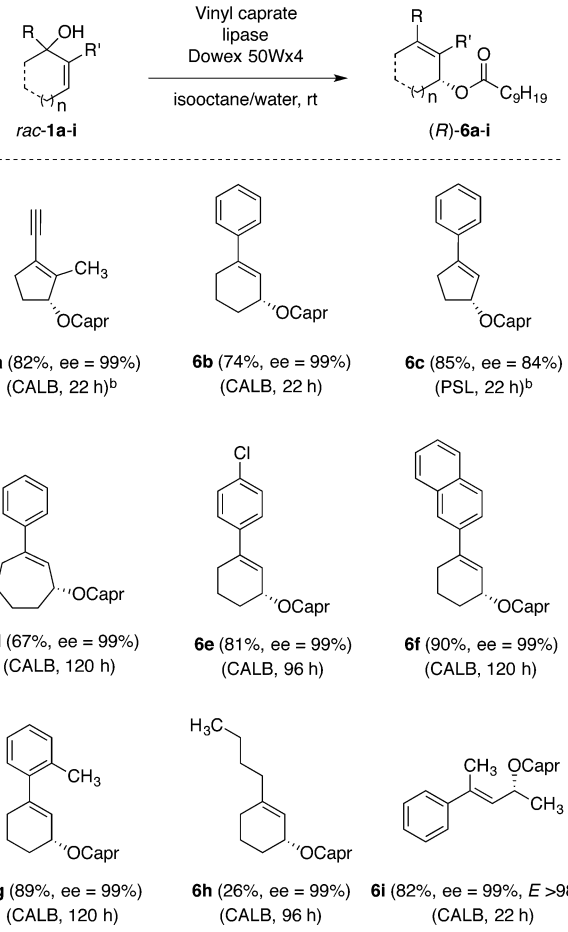
Scheme 2. Influence of Acyl Donor Chain Length on Optical Purity in the Migratory Dynamic Kinetic Resolution



Acyl donor = vinyl acetate: **3b**, R = CH_3 (62%, ee = 81%)
Acyl donor = vinyl butyrate: **5b**, R = C_3H_7 (85%, ee = 95%)
Acyl donor = vinyl caprate: **6b**, R = C_9H_{19} (76%, ee = 99%)

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 10, however, an efficient DKR was obtained and the

Scheme 3. Scope of the Migratory Dynamic Kinetic Resolution[a]



[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 the case of **1a** and **1c**.

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 4 to 5 days not only cycloheptenyl caprate **6d** but also various cyclohexenyl derivatives carrying substituted aryl moieties (**6e–6g**) were obtained in good to excellent yields with 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.

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 (Figure 2). It was possible to reuse

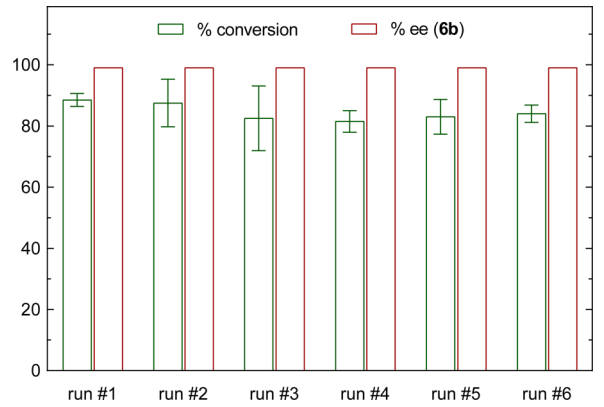


Figure 2. Recyclability of the resin-bound catalysts in the migratory dynamic kinetic resolution of alcohol *rac*-**1b**.

both Dowex 50Wx4 and CALB for more than six rounds of catalysis 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 reimmersed 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 for the caprate **6b** (ee >99%) was achieved.

In summary, by 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 a 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.

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■ 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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