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Highly stereoselective kinetic resolution of α-allenic alcohols: an enzymatic approach

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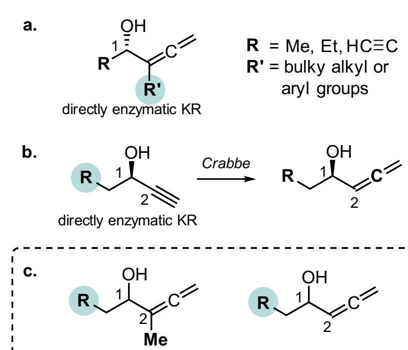
ABSTRACT

A highly efficient lipase AK-catalyzed direct kinetic resolution of a variety of α-allenic alcohols was developed. With the complementary to previous studies, the current reaction system is effective on a broad range of substituents (R^1) at C(1), such as alkyl, aryl, alkenyl, and alkynyl groups. The Jones–Burgess empirical model was modified to interpret the reversed selectivity during the acetylation of secondary alcohol. The methyl group at C(2) of allenic alcohols implied a small structural adjustment in the catalytic triad of lipase AK, representing a potential direction for future site-directed mutagenesis.

Biotransformation has emerged into the chemical arsenal for organic synthesis due to the advantages of high stereoselectivity and relatively simple operations.[1] In particular, enzymatic transesterification and its reverse transformation have found a wide application in numerous syntheses of natural products and pharmaceutically interesting compounds.[2] With the innovative site-directed mutagenesis approach in the past two decades, biotransformation has been expanded into the field of *unnatural* reactions which was conventionally considered as a formidable challenge for natural enzymes.[3] While new and unnatural chemical reactions with enzymes are enrolled into the frontier of biotechnology, defining a new substrate scope remains a useful approach since many enzymes and mutants are commercialized and some of them have been immobilized for the practical use both in academia and industry.[4]

During our study on the development of a non-aldol approach to construct chiral polyol units in biologically significant polyketides,[5] an optical α-allenic alcohol was chosen as the suitable starting material due to its multiple functionalizable sites.[6] Enzymatic kinetic resolution (EKR) of α-allenic alcohols by Novozym 435 resulted in several useful chiral building blocks (Scheme 1a).[7] A variety of groups can be tolerated at C(2) albeit that substituents at C(1) were limited to simple alkyls (methyl, ethyl, or ethynyl). This problem was partially solved when the combination of



Scheme 1. Enzymatic approaches to chiral α-allenic alcohols.

enzymatic resolution of propargylic alcohols[8] and subsequent Crabbé homologation or S_N2' substitution was developed[8f] (Scheme 1b). However, the products bearing a methyl group at C(2) (Scheme 1c) were not feasible from these protocols. Our initial approach on asymmetric cycloisomerization achieved a limited success.[9]

As a particular interest on lipase AK-catalyzed reaction, Burgess and co-workers rationalized the enzymatic kinetic resolution of secondary alcohols.[10] Despite the fitness of secondary alcohols in these empirical models, the state-of-art of various allenic alcohols remains to be scholarly appreciated. We intended to design a new

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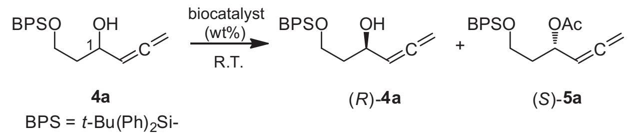
Table 1
Enzymatic kinetic resolution of α-allenic alcohol **4a**[a]



Entry	Biocatalyst	Time (h)	C[c] (%)	(*R*)-**4a** ee%[d]	(*S*)-**5a** ee%[d]	*E*
1	PPL	162[b]	<1	–	–	–
2	PLE	162	<1	–	–	–
3	PS	262	42.7	73.9	99.4	741
4	Novozym 435	162[b]	48.3	43.2	44.2	4
5	CAL-A	262	53.8	99.8	86.4	92
6	CAL-B	162[b]	21.5	13.5	49.7	3
7	CRL	162[b]	13.0	5.7	19.7	2
8	AK	197	50.2	99.6	99.0	1630
9	AK (CH_3CN)	144	37.5	59.1	98.8	303
10	AK (Et_2O)	144	38.9	62.7	99.1	423
11	AK (toluene)	144	45.5	82.7	99.3	741
12	AK (hexane)	72	50.7	98.2	98.8	785
13	AK (octane)	72	50.5	97.6	98.6	632

[a] Standard reaction conditions: biocatalyst (amount: 100 Units, 1–20 mg), alcohol **4a** (0.1 mmol), vinyl acetate (8.0 equiv), solvent (1.0 mL), 23 °C, (^{t}BuOMe for entries 1–8; other solvents indicated in parentheses from entries 9–13). Enantiomeric ratio (E) was calculated according to the equation in Ref 11.
[b] The reaction temperature was 37 °C for 162 h.
[c] C (conversion) = 100 × (ee$_s$/(ee$_s$ + ee$_p$)), ee$_s$ for the recovered starting material, ee$_p$ for the resulting acetate.
[d] Enantiomeric excess (ee) was determined by chiral HPLC. PPL: porcine pancreatic lipase; PLE: pig liver esterase; PS: *Pseudomonas cepacia* lipase; CAL-A: *Candida antarctica* lipase A; CAL-B: *Candida antarctica* lipase B; CRL: *Candida rugosa* lipase.

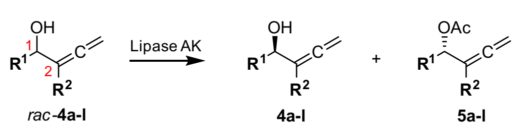
type of substrates to explore EKR, which is compatible with the use of other asymmetric syntheses without a complete new design of catalysis. From this approach, an allene group is considered as a medium group and orientates toward the medium pocket (M) while a variety of substituents may reside in the hydrophobic pocket (L). If this assumption does work, we may readily introduce bulky functional groups in the hydrophobic pocket to expand the scope of enzymatic kinetic resolution in organic synthesis.

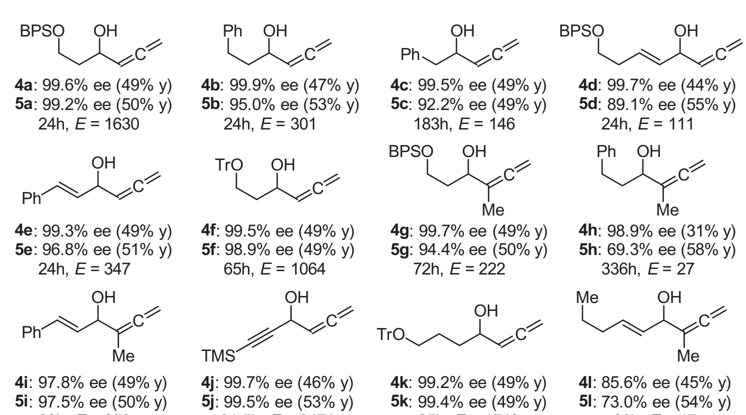
As a model substrate, 1-alkyl allenic alcohol **4a** was subjected to the desired kinetic resolution. Several commercially available lipases were examined (Table 1) and lipase AK (*Pseudomonas fluorescens*) was identified as a superior candidate to match the criteria in terms of the reaction rate, isolated yield, and enantioselectivity of products (enantiomeric ratio $E > 1000$)[11] (entry 8). Although Novozym 435 was very efficient for the kinetic resolution of several α-allenic alcohols as in Ma and Li's report,[7b] it was found less effective on a bulky alkyl substituent at C(1) in **4a** (entry 4, $E = 4$). Lipase PS (*Pseudomonas cepacia* lipase) was found to have a close activity to lipase AK (entry 3, $E = 741$) and would be an alternative catalyst in the future application. Polar solvents (CH_3CN and diethyl ether in entries 9 and 10, respectively) have shown less efficiency than nonpolar solvents (toluene, hexane, and octane) in terms of selectivity and reaction time (entries 11–13).[12] With the consideration of solubility in hydrocarbon solvents, ^{t}BuOMe was then chosen as the reaction media for the optimal conditions (entry 8).

Encouraged by the optimized enzymatic kinetic resolution event, we thus explored the substrate scope, particularly those bearing functional groups at C(1) which could be applied in future polyketide synthesis.[5] The current reaction system offers an excellent stereoselectivity outcome and a broad substrate scope with alkyl substituents at C(1) as well as alkenyl chains (**4a**–**f**, Table 2). The more encouraging C(2)-methylated allenic alcohols are also tolerated and a good resolution was obtained (**4g**–**i**). The less sterically bulky substrate **4h** bearing a flexible side chain displayed a lower selectivity ($E = 27$). Since methylated allenic alcohols cannot be prepared directly from propargylic alcohol through the Crabbé homologation,[13] the generality of enzymatic resolution of mono-substituted and 1,1-disubstituted allenes (R^2 = H or Me) offers a powerful approach to access such synthetically useful building blocks.

The current protocol was also applicable for C(1)-aryl substituted allenic alcohols (Table 3), which was more challenging for

Table 2
Enzymatic kinetic resolution of alkyl and alkenyl substituted α-allenic alcohols **4a**–**l**[a,b14]





[a] Reaction conditions: allenic alcohol **4** (0.5 mmol), lipase AK (25 mg), vinyl acetate (8.0 equiv), ^{t}BuOMe (5.0 mL), 30 °C; enantiomeric excess (ee) was determined by chiral HPLC; isolated yield in parentheses; enantiomeric ratio (E) was calculated according to the equation in Ref. 11.
[b] For substrates **4g**, **4h**, **4i**, and **4l**, the reaction was performed at 37 °C with lipase AK (250 mg). TMS = trimethylsilyl; Tr = triphenylmethyl.