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Kinetic resolution of allylic alcohols via stereoselective acylation catalyzed by lipase PS-30

Peiran Chen [a,b,*], Peng Xiang [a]

[a] School of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 Renmin Road North, Songjiang District, Shanghai 201620, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, CAS, Shanghai 200032, China

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ABSTRACT

By using lipase PS-30 as catalyst, the kinetic resolution of a series of racemic allylic alcohols has been achieved via stereoselective acylation. The value of kinetic enantiomeric ratio (*E*) reached up to 968. Substituent effect is briefly discussed.

Chiral allylic alcohols are among the most versatile synthetic materials as they bear a hydroxyl group and an allylic group on one chiral carbon. Efforts have been made to obtain these compounds. Catalytic enantioselective formation of these chiral building blocks can roughly be divided into two major categories: (1) kinetic resolution (KR) with the Sharpless epoxidation,[1] (2) asymmetric alkenylation of carbonyl compounds.[2]

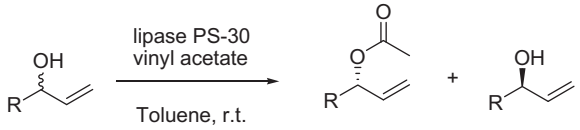
Following by our previous investigation in the kinetic resolution of cyanohydrin catalyzed by the lipase,[3] we are now studying on the stereoselective formation of the allylic alcohols.

In KR, an allylic alcohol racemate are treated by an acylating reagent in the presence of catalyst to stereoselectively obtain an acylated enantiomer and an unreacted enantiomer.[4] Alternatively, acylated allylic alcohol racemate are stereoselectively hydrolyzed in the presence of a lipase or an esterase to give a hydrolyzed enantiomer and an unreacted enantiomer.[4b,5] The theoretical yield of this method is 50% and a pair of enantiomers can be obtained simultaneously.

Racemic allylic alcohol was treated with allyl acetate in the presence of lipase PS-30 (Sigma) in toluene to afford the (*S*)-cyanohydrin acetates and the unreacted (*R*)-cyanohydrins (Scheme 1). To our best knowledge, lipase PS-30 has not been reported being used as a catalyst in the previous allylic alcohol KR literatures. After the consumption of the starting material reached to about 50%, the reaction was stopped and worked up for the enantiomeric excess (ee) value evalution. From the ee values, the values of kinetic enantiomeric ratio (*E*), which is defined in Ref. 6 were calculated.

Table 1 summarizes our results. Some substrates shown in Table 1 (entries 5–7, 10, and 11) are in the first time subjected to KR. The *E* values of seven substrates (entries 1, 3–6, 10, and 11) are close to or larger than 100. According to Schneider et al.[5a] value of $E > 50$ would be sufficient for the production of the desired allylic alcohol acetates in good yield and enantiomeric purity. Results in Table 1 shows that the aryl group containing an electron-withdrawing substituent (entries 3, 5, and 6) increase the *E* values remarkably probably ascribe to their stronger interaction with the enzyme. On the other side, electron-donating substituent on the aryl ring (entries 2 and 7) led to the decrease of *E* values obviously.

Configuration of some acylated products and the acetic derivatization of the unreacted alcohols which were obtained after the allylic alcohol was converted into the corresponding acetate (**2a**[7] and **2k**[2a]) were further proved by comparison of the observed optical rotations of the obtained products with those reported in the literatures (Table 2).



Scheme 1.

* Corresponding author. Tel.: +86 21 67792594.
E-mail address: prchen@dhu.edu.cn (P. Chen).

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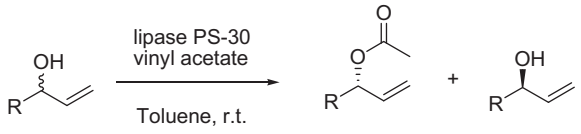
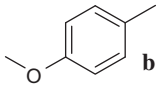
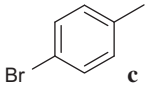
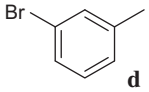
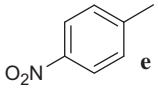
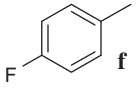
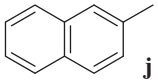
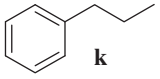
Table 1
Stereoselective acetylation of allelic alcohols **1a–k** with vinyl acetate catalyzed by lipase PS-30



***rac* 1a-k** **2a-k** **3a-k**

Entry	R	ee_E(2)[a] %	ee_A(3)[b] %	*E*[c]	C_{HPLC}[c] (%)	Reaction time (h)
1	 **a**	96.1	63.2	97	46	48
2	 **b**	77.5	12.2	9	34.7	24
3	 **c**	99.3	21.6	352	30	48
4	 **d**	97.5	16.2	93	25	48
5	 **e**	97.1	92.3	227	50	50
6	 **f**	99.7	38.1	968	40	50
7	 **g**	77.8	22.3	10	35	48
8	 **h**	/	/	/	Decomposed	48
9	 **i**	92.3	72.2	54	50	48
10	 **j**	97.1	93.8	241	36	48
11	 **k**	95.4	87	121	50	48

[a] Ee_E stands for enantiomeric excess of allylic alcohol acetate of the fast reacted enantiomer of the allyllic alcohol. Analysis was performed on Chiralcel OJ-H or OD-H column with hexane/*i*-PrOH in varying ratios to afford ee values.
[b] Ee_A stands for enantiomeric excess of the slow reacted enantiomer of the allyllic alcohol, which was obtained after the allyllic alcohol was converted into the corresponding acetate then subjected to chiral HPLC analysis on Chiralcel OD-H column with hexane/*i*-PrOH in varying ratios.
[c] $E = \ln[(1-C_{HPLC})(1-ee_A)]/\ln[(1-C)(1+ee_A)]$, where $C_{HPLC} = ee_A/(ee_E + ee_A)$ as defined in Ref. 6.

Table 2
Configuration assignment of **2a** and **2k** by comparison with the reported $[\alpha]_D$ data

Compound	Measured values		Reported values		Ref.
	$[\alpha]_D$	ee (%)	$[\alpha]_D$	ee (%)	
2a	+30.42(*c* 0.48, $CHCl_3$)	96.06	−25.6(*c* 0.99, $CHCl_3$)	99(*S*)	7
2k[a]	−24.50(*c* 0.58, $CHCl_3$)	95.41	+36.7(*c* 1.31, $CHCl_3$)	91(*R*)	2a

[a] In the case of **2k** (entry 11), the slow reacting enantiomer was assigned to (*S*)-configuration by comparison of the observed optical rotation with the reported literature,[2a] while the fast reacting one to (*R*)-configuration due to the Cahn–Ingold–Prolog rule.

Configuration of the other products (**2b–j**) was proposed to have the same designation as the known ones based on the Kazlauskas' rule.

In conclusion, we have achieved the KR of eleven racemic allylic alcohols via stereoselective acylation using lipase PS-30 as the catalyst. [8] Majority of the substrates gave values of *E* close to or larger than 100, the best one achieves 968.

Acknowledgements

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Supplementary data

Supplementary data (synthetic procedures of the racemic substrates, ^{1}H NMR, ^{19}F NMR spectra, and chiral HPLC chromatography) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.093.

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8. *General KR procedure*: A 5 mL bake-dried vial charged with lipase PS-30 (0.025 g, corresponding to 0.5 mmol of the racemic allyllic alcohols) and two grains of 4 Å molecular sieves was flushed with nitrogen for several minutes, the racemic allyllic alcohols (**1a–k**) dissolved in dried toluene (1 mL) and vinyl acetate (86 mg, 1 mmol) dissolved in dry toluene (1.5 mL) were added. The mixture was stirred at room temperature and analyzed by TLC [petroleum ether/ethyl acetate (20:1–10:1)] until consumption of the starting material was about 50%. The mixture was then filtered and the solid washed with dry acetone (5 mL) and ether (5 mL). The solvent was evaporated in vacuo and the residue was purified on silica gel using petroleum ether/ethyl acetate as the eluent. The unreacted allylic alcohol was acetylated for determination of ee value by adding 0.3 mL of an acetylating solution [anhydrous pyridine (5 mL), acetic anhydride (1 mmol), and DMAP (1% wt/volume)] to 1 mg of the unreacted allelic alcohol. The mixture was stirred at rt for 4 h, washed with saturated aqueous $CuSO_4$ (3×2 mL) to remove pyridine. The solution was dried over $MgSO_4$, concentrated in vacuo and purified by fast column chromatography [petroleum ether/ethyl acetate (20:1)].