Nonenzymatic kinetic resolution of \( \alpha \)-aryl substituted allylic alcohols catalyzed by acyl transfer catalyst \( \text{Np-PIQ} \)

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Abstract

Chiral \( \alpha \)-aryl substituted allylic alcohols are important versatile synthetic intermediates. We report here an effective nonenzymatic kinetic resolution of racemic \( \alpha \)-aryl substituted allylic alcohols by introducing different aryl groups with acyl transfer catalyst \( \text{Np-PIQ} \) and propionic anhydride, providing moderate to good selectivity factors (\( S = 12-37 \)).

1. Introduction

Kinetic resolution (KR) is one of the most powerful strategies for obtaining optically pure compounds.\(^1\) Since Vedejs,\(^2\) Fu\(^3\) and Birman\(^4\) reported the pioneering work on the nonenzymatic acylative KR of secondary alcohols, applying chiral phosphine, chiral 4-dimethylaminopyridine (DMAP) equivalents and chiral amidine derivatives as nucleophilic acyl transfer catalysts respectively, the asymmetric nucleophilic acyl transfer catalysis for the KR of various secondary alcohols has been further developed.\(^5\) Several nucleophilic catalysts have been designed in our group,\(^6\) such as Fc-PIP, Np-PIQ and An-PIQ, which all showed excellent stereoselectivities (\( S \) up to \( >1800 \)) in acylative KR of arylalkyl carbinols.

Chiral allylic alcohols in optically enriched forms are useful intermediates, which could be transformed into different kinds of derivatives by epoxidation, oxidation, reduction, etc.\(^7\) Much effort has been made towards the development of excellent nonenzymatic catalysts for the KR of sec-alcohol substrates. However, the acylative KR of secondary allylic alcohols has received much less attention than that of the other sec-alcohols,\(^8\) probably due to the weakness of \( \pi-\pi \) stacking interaction and \( \pi \)-cation interaction between the carbon–carbon double bond and the acylated catalyst.

During the past decades, several kinds of substrates have been investigated, such as secondary cinnamyl alcohols, aryl alkenylcarbinols, polysubstituted allylic alcohols and Baylis-Hillman adducts (Fig. 1). However, the nucleophilic nonenzymatic KR of \( \alpha \)-aryl substituted allylic alcohols has rarely been employed, and the only two substrates showed the low selectivity factors of 14\(^8\) and 11\(^8\).

Fig. 1. Nucleophilic nonenzymatic acylative KR of allylic alcohols.

Herein, we would like to disclose an effective nonenzymatic KR of a series of racemic secondary allylic alcohols with \( \alpha \)-aryl groups utilizing acyl transfer catalyst \( \text{Np-PIQ} \), providing corresponding unreacted alcohols and acylated products with moderate to good selectivity factors (\( S = 12-37 \)).

2. Results and discussion

Initially, \( \text{rac-1a} \) was chosen as the model substrate to investigate the feasibility of the asymmetric KR with different nucleophilic catalysts (Table 1). The reaction underwent smoothly when our newly developed catalyst \( \text{Np-PIQ} \) was used as the nucleophilic...
Further screening of anhydrides revealed that propionic anhydride was optimal for the acylative kinetic resolution, whereas other anhydrides displayed much lower selectivity factor and activity compared to aliphatic anhydrides (Table 3, entries 3 vs 3–5). The effect of TEA on selectivity factor of the kinetic resolution was also examined, and found slightly inferior to DIPEA in terms of both stereoselectivity and conversion (Table 3, entries 2 vs 1).

Optimization of nucleophilic catalysts, solvents, anhydrides and bases led us to establish that 5.0 mol\% Np-p-PIQ/(EtCO)\textsubscript{2}O (0.75 equiv)/DIPEA (0.75 equiv)/MTBE/CHCl\textsubscript{3} (v/v=1:1) (0.1 M) 0°C were the optimal reaction conditions for the catalytic kinetic resolution. Under these conditions, the generality and scope of the secondary allylic alcohols kinetic resolution were investigated, and the results are summarized in Table 4.

The kinetic resolution of a wide array of allylic alcohols 1 with electron-neutral, electron-deficient or electron-rich substituents on the aromatic ring proceeded smoothly under the optimal reaction conditions, providing moderate to good selectivity factors (S=12–37) (Table 4). The positions of substituents attached to the aromatic ring had significantly effects on selectivity factor and activities. para-Methoxyl phenyl substituted allylic alcohol 1b displayed higher selectivity factor and activity compared to meta- and ortho-methoxyl phenyl substituted allylic alcohol 1e and 1d (Table 4, entries 2–4). Notably, naphthyl substituted alkenyl carbinols were also tolerated, and 2-naphthyl substituted alkenyl carbinol 1j...
showed better selectivity and activity than 1-naphthyl substituted alkyl carbinal 1k, probably due to the different reinforcement of π-stacking interactions between the substrate and the acylated catalyst (Table 4, entries 10, 11). Furthermore, the bulky alkyl groups R² resulted in lower activity even in 48 h due to the steric hindrance (Table 4, entry 12).

Comparing with the KR of allylic alcohols without aryl groups reported previously, better results were obtained with these secondary allylic alcohols 1, probably due to the better selectivity and activity of our newly developed catalyst Np-PiQ and/or the synergistic effect of acylated catalyst, aryl group and carbon—carbon double bond of the substrate, which would make the interaction between the substrate and intermediate much stronger.

3. Conclusion

In conclusion, we developed an effective nonenzymatic kinetic resolution of racemic α-aryl substituted allylic alcohols by introducing different aryl groups with acyl transfer catalyst Np-PiQ and propionic anhydride, and moderate to good selectivity factors were observed (5–12–37). Meanwhile, this protocol also provides a complementary method for the asymmetric synthesis of secondary allylic alcohols.

4. Experimental section

4.1. General

All reagents and starting materials were obtained commercially and used as received unless otherwise specified. The substrates used in the kinetic resolution experiments were prepared by Bayliss-Hillman reaction. Solvents and reagents were dried in advance. Catalyst An-PiQ, Np-PiQ, Fc-PiQ, (R)-BTM were synthesized according to literature procedures.

1H NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in chloroform-d. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s=single, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad single, coupling constant(s) in Hertz, integration). 13C NMR spectra were recorded on a Bruker DPX 100 MHz spectrometer in chloroform-d. Chemical shifts are reported in parts per million with the internal chloroform signal at 77.0 ppm as a standard.

Methods used for kinetic resolution experiments determination of ee’s and calculation of conversions and selectivities were adopted from previously published work. Enantiomeric ratios were determined by HPLC, using a Diacel CHIRALCEL OD-H column and a Diacel IF-H column with hexane and i-ProH as eluents. Selectivity factors and conversions were calculated from the enantiomeric excess values of the ester products and the recovered unreacted alcohol substrates according to Kagan’s equations.

4.2. General experimental procedure

Under nitrogen atmosphere, catalyst Np-PiQ (0.01 mmol), racemic secondary alcohol (0.2 mmol), DIPEA (0.15 mmol), MTBE (1 mL) and CHCl₃ (1 mL) were sequentially added to a 10 mL flame-dried Schlenk tube in an ice bath. After stirring at 0 °C for 5 min, the reaction mixture was treated with propionyl anhydride (0.15 mmol). Then the resulting solution was stirred at 0 °C for the specified time and further quenched by rapid addition of methanol (0.2 mL). The solution was warmed to room temperature and stirred for an additional 2 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (5%–10% EtOAc/petroleum) to separate the ester from the unreacted alcohol.

4.3. The preparation of allylic alcohols

To a stirred solution of phenyl-2-propanone (10 equiv) in DMF was successively added paraformaldehyde (50 equiv), piperidine (1.3 equiv) and AcOH (2.2 equiv). The resulting mixture was heating at 90 °C for 1 h. After cooling, water was added to the residue and the mixture was extracted with EA. The combined organic layers were washed with water, dried over MgSO₄, filtered, and concentrated to give in vacuo vinyl ketone. To a solution of vinyl ketone (1 equiv) in methanol at 0 °C were added cerium trichloride (1 equiv) and sodium borohydride (1 equiv). The reaction mixture was stirred for 15 min at 0 °C and then saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the allylic alcohols 1.

4.3.1. 3-Phenylbut-3-en-2-ol (1a). Colorless oil, 85% yield; 1H NMR (400 MHz, CDCl₃): δ 7.43–7.26 (m, 5H), 5.36 (s, 1H), 5.28 (s, 1H), 4.82 (q, J=6.3 Hz, 1H), 1.84 (s, 1H), 1.32 (d, J=6.4 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 100/5 hexane/i-ProH, λ=254 nm, retention time: (S) 8.1 min, (R) 10.3 min).

4.3.2. 3-(4-Methoxyphenyl)but-3-en-2-ol (1b). Colorless oil, 87% yield; 1H NMR (400 MHz, CDCl₃): δ 7.43–7.33 (m, 2H), 6.94–6.85 (m, 2H), 5.31 (t, J=12 Hz, 1H), 5.25 (s, 1H), 4.86–4.78 (m, 1H), 3.84 (s, 3H), 1.73 (s, 1H), 1.35 (d, J=6.4 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 100/5 hexane/i-ProH, λ=254 nm, retention time: (S) 10.1 min, (R) 11.5 min).

4.3.3. 3-(3-Methoxyphenyl)but-3-en-2-ol (1c). Colorless oil, 91% yield; 1H NMR (400 MHz, CDCl₃): δ 7.26 (t, J=7.9 Hz, 1H), 7.06–6.90 (m, 2H), 6.85 (dd, J=8.3, 1.8 Hz, 1H), 5.36 (s, 1H), 5.29 (s, 1H), 4.85–4.75 (m, 1H), 3.82 (s, 3H), 1.74 (s, 1H), 1.33 (d, J=6.4 Hz, 3H). 13C NMR (100 MHz, CDCl₃): δ 159.6, 153.0, 141.5, 129.4, 119.3, 112.9, 112.8, 111.7, 69.5, 55.2, 22.6. HRMS (El, m/z): Calcd for C₁₁H₁₄O₂: 178.0994, found: 178.0993. The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 90/10 hexane/i-ProH, λ=254 nm, retention time: (S) 7.9 min, (R) 11.2 min).

4.3.4. 3-(2-Methoxyphenyl)but-3-en-2-ol (1d). Colorless oil, 87% yield; 1H NMR (400 MHz, CDCl₃): δ 7.34–7.22 (m, 2H), 7.12 (d, J=6.9 Hz, 1H), 7.01–6.83 (m, 2H), 5.46 (s, 1H), 5.08 (s, 1H), 4.69 (s, 1H), 3.84 (s, 3H), 2.53 (s, 1H), 1.23 (d, J=6.3 Hz, 3H). 13C NMR (100 MHz, CDCl₃): δ 152.5, 151.7, 129.9, 129.0, 127.9, 119.9, 113.1, 109.6, 69.2, 54.5, 213. HRMS (El, m/z): Calcd for C₁₁H₁₄O₂: 178.0994, found: 178.0995. The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 90/10 hexane/i-ProH, λ=254 nm, retention time: (S) 6.2 min, (R) 9.7 min).

4.3.5. 3-(3,4-Dimethoxyphenyl)but-3-en-2-ol (1e). White solid, mp 39–40 °C, 86% yield; 1H NMR (400 MHz, CDCl₃): δ 6.96 (s, 2H), 6.84 (d, J=8.5 Hz, 1H), 5.31 (s, 1H), 5.24 (s, 1H), 4.80 (s, 1H), 3.90 (s, 3H), 3.89 (3H), 1.73 (s, 1H), 1.34 (d, J=6.3 Hz, 3H). 13C NMR (100 MHz, CDCl₃): δ 151.6, 147.7, 131.1, 131.8, 110.0, 109.6, 109.4, 68.6, 54.9, 215. HRMS (El, m/z): Calcd for C₁₂H₁₄O₃: 208.1099, found: 208.1100. The ee was determined by HPLC (Chiralcel IF,
1 mL/min, 40/1 hexane/i-PrOH, λ=254 nm, retention time: (S) 36.4 min, (R) 39.6 min).

3.4.6. 3-(3,4,5-Trimethoxyphenyl)but-3-en-2-ol (1T). White solid, mp 53–55 °C, 89% yield; [1H NMR (400 MHz, CDCl3)]: δ 7.29 (d, J=8.0 Hz, 2H), 7.15 (d, J=7.9 Hz, 2H), 5.32 (s, 1H), 5.26 (s, 1H), 4.88–4.72 (m, 1H), 2.35 (s, 3H), 1.72 (d, J=3.9 Hz, 1H), 1.32 (d, J=6.4 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 100/5 hexane/i-PrOH, λ=254 nm, retention time: (S) 7.3 min, (R) 7.9 min).

3.4.7. 3-(p-Toly)but-3-en-2-ol (1g). Colorless oil, 90% yield; [1H NMR (400 MHz, CDCl3)]: δ 7.91–7.90 (m, 5H), 7.58–7.57 (m, 4H), 7.50 (s, 1H), 5.41–5.39 (m, 1H), 4.89 (q, J=6.4 Hz, 1H), 2.49 (t, J=7.3 Hz, 2H), 1.74 (d, J=6.4 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 100/5 hexane/i-PrOH, λ=254 nm, retention time: (S) 16.3 min, (R) 18.0 min).

3.4.8. 3-(4-Chlorophenyl)but-3-en-2-ol (1h). Colorless oil, 87% yield; [1H NMR (400 MHz, CDCl3)]: δ 8.20 (d, J=8.9 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H), 5.54 (s, 1H), 5.42 (s, 1H), 4.84 (q, J=6.4 Hz, 1H), 1.77 (s, 1H), 1.34 (d, J=4.6 Hz, 3H). [13C NMR (100 MHz, CDCl3)]: δ 151.1, 147.2, 146.6, 127.8, 123.6, 115.1, 69.4, 22.6. [HRMS (El,m/z): Calcd for C10H15NO: 193.0739, found: 193.0742. The ee was determined by HPLC (Chiralcel OD, 1.0 mL/min, 40/1 hexane/i-PrOH, λ=254 nm, retention time: (S) 16.4 min, (R) 20.8 min).

3.4.9. 3-(4-Nitrophenyl)but-3-en-2-ol (1i). White solid, mp 41–43 °C, 67% yield; [1H NMR (400 MHz, CDCl3)]: δ 7.91–7.80 (m, 4H), 7.58 (d, J=8.6, 1.4 Hz, 1H), 7.55–7.46 (m, 2H), 5.50 (s, 1H), 5.45 (s, 1H), 5.01–4.92 (m, 1H), 1.83 (s, 1H), 1.41 (d, J=6.4 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 0.8 mL/min, 40/1 hexane/i-PrOH, λ=254 nm, retention time: (S) 17.2 min, (R) 18.9 min).

3.4.10. 3-(Naphthalen-2-yl)but-3-en-2-ol (1j). White solid, mp 58–60 °C, 91% yield; [1H NMR (400 MHz, CDCl3)]: δ 8.02 (d, J=5.0 Hz, 1H), 7.86 (d, J=4.5 Hz, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.52–7.50 (m, 3H), 7.31 (d, J=6.9 Hz, 1H), 5.72 (s, 1H), 5.18 (s, 1H), 4.72 (s, 1H), 1.79 (s, 1H), 1.28 (d, J=6.3 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 40/1 hexane/i-PrOH, λ=254 nm, retention time: (S) 9.9 min, (R) 11.2 min).

3.4.11. 4-Methyl-2-phenylpent-1-en-3-ol (1k). Colorless oil, 85% yield; [1H NMR (400 MHz, CDCl3)]: δ 7.45–7.20 (m, 5H), 5.32 (s, 2H), 4.40 (s, 1H), 1.82–1.68 (m, 2H), 0.91 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H). The ee was determined by HPLC (Chiralcel OD, 1 mL/min, 100/5 hexane/i-PrOH, λ=254 nm, retention time: (S) 5.9 min, (R) 8.9 min).

4.4. The determination of ester’s ee value

The enantiomeric excesses of the esters were determined by hydrolysis to the parent alcohols (2 mL of 2 M KOH in methanol, at room temperature until complete by TLC), which were analyzed as described above.

The conversions and selectivities were calculated as:

\[
\text{Conversion} = \frac{C_{\text{Initial}} - C_{\text{Final}}}{C_{\text{Initial}}} \times 100\%
\]

\[
\text{Selectivity} = \frac{C_{\text{Product}}}{C_{\text{Initial}}} \times 100\%
\]

where \(C_{\text{Initial}}\) is the concentration of the reactant, and \(C_{\text{Product}}\) is the concentration of the product.

The enantiomeric excess of the ester and \(e_{A}\) is the enantiomeric excess of the unreacted alcohol.

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Supplementary data

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