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Ruthenium-Catalyzed Enantioselective Reduction of Electron-Rich Aryl Alkyl Ketones

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Abstract: Presented here is the investigation of the transfer hydrogenation of electron-rich aryl alkyl ketones using ruthenium complexes of dipeptide-like ligands and 2-propanol as hydride source. The reduction proceeded with excellent selectivity (up to > 99% *ee*) and in moderate to high yields (up to 90%).

Keywords: asymmetric catalysis; hydrogen transfer; ketones; reduction; ruthenium

Introduction

The asymmetric reduction of prochiral ketones using transfer-hydrogenation is an effective and mild route for the formation of optically active secondary alcohols.[1] Replacing the aluminium alkoxides initially used to mediate the Meerwein–Ponndorf–Verley reduction[2] with transition metal complexes opened the field for a more efficient ketone reduction. Among the various transition metals used, ruthenium-based complexes have shown particularly high catalytic activity, especially in the presence of a base that promotes the formation of the active ruthenium hydride catalysts.[3,4] The development of chiral ruthenium complexes based on phosphine ligands allowed for the formation of enantiomerically enriched alcohols,[5] however, the major breakthrough regarding high enantioselectivity came with the introduction of novel ruthenium-arene-based catalysts. Noyori and co-workers found that ruthenium-arene complexes combined with either vicinal amino alcohols or mono-tosylated 1,2-diamines (e.g., TsDPEN) worked as highly efficient and selective catalysts for the reduction of a variety of prochiral ketones using either 2-propanol or formic acid/triethylamine as the reducing agent.[6] The initial discovery by Noyori started an intensive search for other catalysts based on the same concept. A number of enantiomerically pure 1,2-amino alcohols were found to act as efficient ligands in the transformation, but the ruthenium-arene complex of TsDPEN remains as one of the best catalysts for the reduction of ketones.[7] Apart from diamine-based ligands, Zhang and co-workers introduced chiral tridentate bis-oxazoline ligands which, upon complexation with ruthenium salts, resulted in highly active and enantioselective catalysts for the reduction of aryl alkyl ketones.[8] Inspired by the results obtained by Zhang, we investigated the catalytic ability of a number of ruthenium complexes based on *N*-functionalized 2-aminomethyloxazoline derivatives.[9] The results were rather poor, but interestingly we found that a Boc-protected amino acid hydroxy-amide, a precursor to the 2-aminomethyloxazolines, acted as an efficient ligand in the transfer hydrogenation. The combination of $[RuCl_2(p\text{-cymene})]_2$ and ligands **1** or **2** generated ruthenium complexes which catalyzed the reduction of aryl alkyl ketones in good yield and in excellent enantioselectivity.[10] The simplicity of the ligand structure and the high availability of α-amino acids and 1,2-amino alcohols enabled a fast screening of libraries of ligands for the transfer hydrogenation of ketones. We found that the most efficient and selective catalysts were obtained using the alanine-based ligands **1a** or **2a** (Figure 1), with the latter leading to slightly better activity and selectivity. Furthermore, we found that protection of the *N*-terminal with a carbamate protecting group (Boc, Alloc or Cbz) was crucial, since no catalytic activity was observed using the unprotected compound. No reaction occurred with ligands lacking the hydroxy group or when the alcohol was protected by *O*-methylation. Hence it is obvious that the structural integrity of the *N*-protected amino acid hydroxy-amide ligand must remain intact.

Results and Discussion

During our investigation on the reduction of a range of aryl alkyl ketones, we observed that electron rich

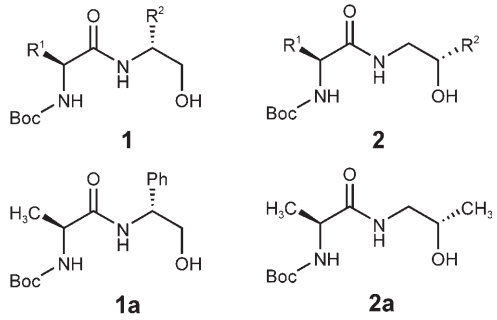
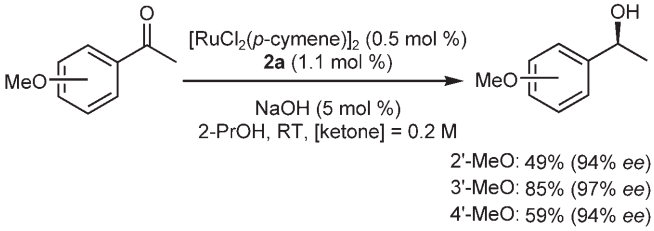


Figure 1.

substrates (e.g., methoxy-substituted acetophenones) were readily reduced to give the corresponding alcohol in high *ee*s (Scheme 1).[10c] Regarding reactivity,



Scheme 1. Asymmetric transfer hydrogenation of electron-rich methoxyacetophenones.

we observed significant differences depending on the aryl substitution pattern. 3′-Methoxyacetophenone reacted readily and the product was obtained in high yield, whereas the 2′- and 4′-methoxyacetophenones were reduced only with moderate conversions (50–60%). The poor reactivity of 2′- and 4′-methoxyacetophenones can be explained by electronic effects although, according to the reported reduction potentials of these ketones, the order of reactivity is expected to be somewhat different.[11]

Nevertheless, the high enantiomeric excess obtained in the reduction of acetophenones substituted with electron-donating groups prompted us to extend the investigation to other electron-rich acetophenones. Their corresponding alcohols are present in numerous biologically active compounds like the top-selling pharmaceuticals (*R*)-denopamine (**3**),[12] salmeterol (**4**)[13] and terbutaline (**5**)[14] (Figure 2). The direct reduction of the ketones leading to compounds like **3–5** can, however, be difficult due to their additional functionality and possible chelating abilities.

Hence, with this objective in mind we set out to screen a number of different acetophenones substituted with electron-donating groups (Table 1). Di- and tri-substituted acetophenones were readily reduced in yields ranging from 40 to 90% (entries 1–6, Table 1). As we previously observed in the reduction of mono-

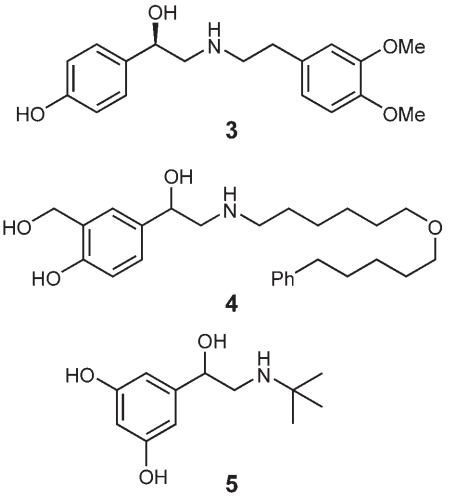
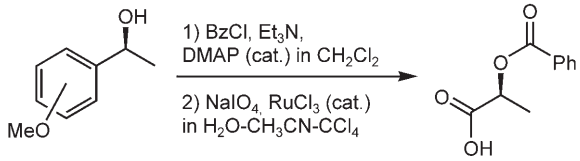


Figure 2.



Scheme 2. Synthesis of (*S*)-(+)-*O*-benzoyl lactic acid for absolute configuration determination.

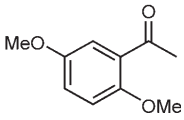
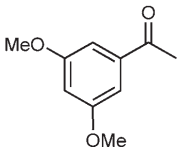
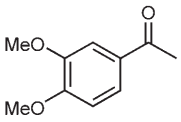
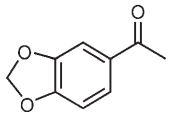
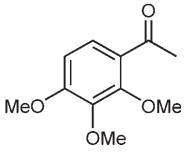
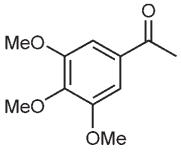
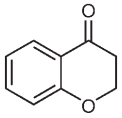
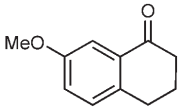
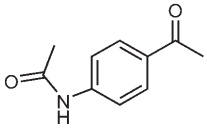
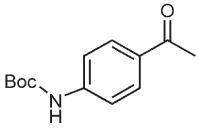
substituted acetophenones, a methoxy-functionality in the *ortho*- or *para*-position resulted in lower yields compared to the *meta*-analogue. Interestingly, the di- and tri-substituted ketones were reduced with excellent *ee*s regardless of the substitution pattern. The cyclic ketones 4-chromanone and 7-methoxytetralone were reduced with excellent enantioselectivity and in moderate yields (entries 7 and 8). Additionally, we attempted to reduce 4′-aminoacetophenone, however, we observed poor conversion (<15%), and moderate enantioselectivity. Reductions of the corresponding *N*-acetyl- or *N*-Boc-protected substrates gave the secondary alcohols in high enantioselectivity (entries 9 and 10).

The absolute configurations for the new alcohols were determined using oxidative degradation of the aromatic system according to the procedure described in Scheme 2, and the obtained product was compared to (*S*)-(+)-*O*-benzoyllactic acid.[15]

Conclusions

We have demonstrated that the ruthenium-arene *pseudo*-dipeptide complexes catalyze the reduction of electron-rich aryl alkyl ketones with excellent enantioselectivity (up to >99% *ee*). The simplicity of the method in combination with the highly modular and

Table 1. Enantioselective reduction of electron-rich aryl methyl ketones.[a]

Entry	Substrate	Time [h]	Yield[b] [%]	*ee*[c] [%]
1		2.5	69	96 (*S*)
2		2	90	97 (*S*)
3		2.5	58	98 (*S*)
4		2.5	65	95 (*S*)
5[d]		2.5	39	95 (*R*)
6[e]		2.5	84	99 (*S*)
7[d]		3	59	>99 (*R*)
8[f]		2.5	42	98 (*S*)
9[e,f]		3	31	95 (*S*)
10[e,f]		3	43	96 (−)

[a] Reactions conditions: ketone (5 mmol, 0.2 M in 2-propanol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol% in Ru, 15.2 mg), **2a** (1.1 mol%) and NaOH (5 mol%, 0.09 M solution in 2-PrOH). All reactions were performed at room temperature.
[b] Isolated yields.
[c] Enantiomeric excess was determined by GC (CP Chirasil DEX CB) and the absolute configuration was determined from the sign of optical rotation, or *via* oxidative degradation as described below (Scheme 2).
[d] ***ent*-2a** was used as ligand.
[e] NaO-*i*-Pr (5 mol%, 0.1 M solution in 2-PrOH) was used as base.
[f] Enantiomeric excess values were determined by HPLC on Chirasil AD or AS columns.

readily available, inexpensive *N*-protected amino acid hydroxy-amide ligands make this protocol very attractive.

Experimental Section

General Procedure for the Transfer Hydrogenation of Electron-Rich Ketones Presented in Table 1

Ligand **2a** (13.5 mg, 0.055 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.2 mg, 0.025 mmol, catalyst loading: 1 mol%) were dried under vacuum in a dry Schlenck tube for 15 min. 2-Propanol (22.5 mL) and 2.5 mL of 0.1 M solution of *i*-PrONa (5 mol%) were added under a nitrogen atmosphere. The solution was stirred for 5 min and the ketone (5 mmol) was added. The reaction mixture was stirred at room temperature for time stated in Table 1. The reaction was quenched by addition of aqueous NH_4Cl, extracted with EtOAc and the organic phase was subsequently passed through a pad of silica and evaporated under vacuum. The products were purified using SiO_2 column chromatography. The *ee* of the products were analyzed by GLC (CP Chirasil DEX CB) or HPLC (AD or AS chiral columns).

(*S*)-1-(2,5-Dimethoxyphenyl)ethanol[16] (Table 1, entry 1): Yield: 69%; 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.8$ Hz, 3H), 2.63 (s br, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 5.06 (m, 1H), 6.75 (dd, $J = 8.8$ Hz, $J = 3.2$ Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.94 (d, $J = 3.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.2$, 55.9, 56.0, 66.8, 111.6, 112.5, 112.7, 134.9, 150.9, 154.0; GLC (CP Chirasil DEX CB): 110 °C hold for 0 min, rate 20 °C min^{-1} to 130 °C and hold for 30 min, rate 1 °C min^{-1} to 135 °C, rate 20 °C min^{-1} to 200 °C and hold for 5 min: t_R(*R*-isomer) = 22.7 min, t_R(*S*-isomer) = 24.9 min; $[\alpha]_D^{20}$: −29.6 (*c* 5, $CHCl_3$) {lit.[16] $[\alpha]_D$: −25.8 (*c* 0.9, $CHCl_3$), > 95% *ee*}.

(*S*)-1-(3,5-Dimethoxyphenyl)ethanol[17] (Table 1, entry 2): Yield: 90%; 97% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$ (d, $J = 7.2$ Hz, 3H), 1.80 (s br, 1H), 3.81 (s, 6H), 4.83 (q, $J = 8.1$ Hz, 1H), 6.38 (t, $J = 1.0$ Hz, 1H) 6.53 (d, $J = 1.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$, 55.6 (2C), 70.7, 99.6, 103.5 (2C), 148.7, 161.2; GLC (CP Chirasil DEX CB): 110 °C hold for 0 min, rate 20 °C min^{-1} to 130 °C and hold for 30 min, rate 1 °C min^{-1} to 135 °C, rate 20 °C min^{-1} to 200 °C and hold for 5 min: t_R(*R*-isomer) = 29.2 min, t_R(*S*-isomer) = 30.2 min; $[\alpha]_D^{20}$: −32.7 (*c* 2.0, $CHCl_3$); the absolute configuration determined as presented below.

(*S*)-1-(3,4-Dimethoxyphenyl)ethanol[15] (Table 1, entry 3): Yield: 58%; 98% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.3$ Hz, 3H), 1.93 (s br, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.83 (q, $J = 6.3$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 6.89 (dd, $J = 8.1$ Hz, $J = 0.9$ Hz, 1H), 6.93 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$, 56.0, 56.2, 70.4, 108.9, 111.2, 117.7, 138.8, 148.6, 149.3; GLC (CP Chirasil DEX CB): 110 °C hold for 2 min, rate 1 °C min^{-1} to 131 °C, hold for 0 min, rate 80 °C min^{-1} to 200 °C and hold for 5 min: t_R(*R*-isomer) = 24.44 min, t_R(*S*-isomer) = 25.03 min; $[\alpha]_D^{20}$: −38.3 (*c* 2.85, $CHCl_3$) {lit.[18] $[\alpha]_D$: +40.5 (*c* 1.1, $CHCl_3$), 97% *ee R*-isomer}.

(*S*)-1-(3,4-Methylenedioxyphenyl)ethanol[15] (Table 1, entry 4): Yield: 65%; 95% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.45$ (d, $J = 6.4$ Hz, 3H), 1.8 (s br, 1H), 4.82 (q, $J = 5.6$ Hz, 1H), 5.94 (s, 2H), 6.76 (dd, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H), 6.81 (dd, $J = 8.1$ Hz, $J = 1.6$ Hz, $J = 0.4$ Hz, 1H), 6.89 (dd, $J = 1.6$ Hz, $J = 0.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$, 70.5, 101.2, 106.3, 108.3, 118.9, 140.2, 147.1, 148.0; GLC (CP Chirasil DEX CB):110 °C hold for 2 min, rate 1 °C min^{-1} to 131 °C, hold for 0 min, rate 80 °C min^{-1} to 200 °C and hold 5 min: t_R(*R*-isomer) = 18.49 min, t_R(*S*-isomer) = 19.03 min; $[\alpha]_D^{20}$: −40 (*c* 2.1, $CHCl_3$) {lit.[15] $[\alpha]_D$: +46.5 (*c* 1.01, $CHCl_3$), 97% *ee R*-isomer}.

(*R*)-1-(2,3,4-Trimethoxyphenyl)ethanol[19] (Table 1, entry 5): Yield: 39%; 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.8$ Hz, 3H), 2.41 (s br, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 5.05 (m, 1H), 6.66 (d, $J = 8.8$ Hz, 1H) 7.03 (d, $J = 8.8$ Hz , 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.7$, 55.9, 60.6, 61.1, 65.8, 107.1, 120.3, 131.2, 141.9, 151.0, 153.0; GLC (CP Chirasil DEX CB): 110 °C hold 0 min, rate 20 °C min^{-1} to 130 °C, hold 30 min, rate 1 °C min^{-1} to 135 °C, rate 20 °C min^{-1} to 200 °C and hold for 5 min; $[\alpha]_D^{20}$: +20.8 (*c* 3.6, $CHCl_3$); absolute configuration determined as presented below.

(*S*)-1-(3,4,5-Trimethoxyphenyl)ethanol[19] (Table 1, entry 6): Yield: 84%; 99% ee; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.4$ Hz, 3H), 1.81 (s, br, 1H), 3.84 (s, 3H), 3.88 (s, 6H), 4.84 (m, 1H), 6.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.2$, 56.0, 60.7, 70.5, 102.2, 137.0, 141.7, 153.2; GLC (CP Chirasil DEX CB): 110 °C, hold 2 min, rate 20 °C min^{-1} to 159 °C, hold 0 min, rate 0.3 °C min^{-1} to 164 °C, 20 °C min^{-1} to 200 °C, hold 10 min: t_R(*R*-isomer) = 12.38 min, t_R (*S*-isomer) = 12.15 min; $[\alpha]_D^{20}$: −27.8 (*c* 2.8, $CHCl_3$); absolute configuration determined as presented below.

(*R*)-4-Chromanol [(*R*)-3,4-dihydro-2*H*-1-benzopyran-4-ol][20] (Table 1, entry 7): Yield: 59%; > 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.82$ (m, 1H), 2.01–2.18 (m, 2H), 4.26–4.29 (m, 2H), 4.79 (m, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.92 (m, 1H), 7.21 (m, 1H), 7.31 (d, $J = 7.69$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.8$, 61.9, 63.3, 117.1, 120.6, 124.3, 129.6, 129.7, 154.6; GLC (CP Chirasil DEX CB): 110 °C, hold 0 min, rate 20 °C min^{-1} to 125 °C, hold 0 min, rate 0.5 °C min^{-1} to 135 °C, hold 0 min, rate 20 °C min^{-1} to 200 °C, hold 5 min: t_R(*R*-isomer) = 16.57 min, t_R(*S*-isomer) = 16.91 min; $[\alpha]_D^{20}$: +65 (*c* 1.0, $CHCl_3$) {lit.[20] $[\alpha]_D$: −67.45(*c* 0.5, EtOH), 98% *ee*, *S*-isomer}.

(*S*)-1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenol[21] (Table 1, entry 8): Yield: 42%; 98% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.57$–2.03 (m, br, 5H), 2.63–2.78 (m, br, 2H), 3.80 (s, 3H), 4.75 (m, 1H), 6.78 (m, 1H), 6.99–7.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.2$, 28.4, 32.4, 55.3, 68.5, 112.6, 114.4, 129.1, 129.9, 139.8, 158.0; HPLC (AD) 2% 2-propanol in hexane, 0.5 mL min^{-1}, t_R(*S*-isomer) = 59 min, t_R(*R*-isomer) = 67 min; $[\alpha]_D^{20}$: +43.5 (*c* 1.05, $CHCl_3$); {lit.[21] $[\alpha]_D$: +45.8 (*c* 3.63, $CHCl_3$), 100% ee}.

(*S*)-*N*-[4-(1-Hydroxyethyl)phenyl]acetamide[22] (Table 1, entry 9): Yield: 31%; 95% *ee*; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.44$ (d, $J = 6.6$ Hz, 3H), 2.13 (s, 3H), 4.81 (q, $J = 6.6$ Hz, 1H), 7.32 (d, $J = 8.4$, 2H), 7.52 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 23.9$, 25.6, 70.6, 121.3, 127.1, 139.0, 143.5, 171.7; HPLC (AD) 2% 2-propanol in hexane, 0.5 mL min^{-1}, t_R(*S*-isomer) = 47.2 min, t_R(*R*-isomer) = 50.1 min; $[\alpha]_D^{20}$: −40.6 (*c* 0.75, $CHCl_3$).

(−)-*N*-(*tert*-Butyloxycarbonyl)-4-amino-1-phenylethanol[23] (Table 1, entry 10): Yield: 43%; 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (d, $J = 6.6$ Hz, 3H), 1.51 (s, 9H), 1.55 (br s, 1H), 4.84 (q, $J = 6.6$ Hz, 1H), 6.45 (br s, 1H), 7.29–7.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.0$, 28.3, 69.9, 80.5, 118.6, 126.0, 137.6, 140.5, 152.8; HPLC (AS) 10% 2-propanol in cyclohexane, 0.5 mL min^{-1}, t_R(major isomer) = 44.4 min, t_R(minor isomer) = 60.6 min; $[\alpha]_D^{20}$: −30 (*c* 0.5, $CHCl_3$).

General Procedure for the Preparation of (*S*)-(+)-*O*-Benzoyllactic Acid

Benzoylation: 1 mmol of the chiral alcohol was dissolved in 18 mL DCM. Triethylamine (0.7 mL, 5 mmol) was added followed by benzoyl chloride (0.5 mL, 4.3 mmol) and then DMAP (10.4 mg, 0.08 mmol). The reaction mixture was left overnight and was then diluted with DCM and was washed with 1) ice/water, 2) 1M HCl, 3) water. The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by SiO_2 column chromatography (10:1, toluene:EtOAc) afforded a 70% yield of the benzoylated product.

Oxidative cleavage: 0.5 mmol of the benzoylated alcohol was dissolved in $CCl_4/CH_3CN/H_2O$ (1 mL:1 mL:1.5 mL). $NaIO_4$ (1.4 g, 6.4 mmol) was added followed by $RuCl_3 \cdot H_2O$ (8 mg, 0.04 mmol). After 4 days stirring the mixture was diluted with DCM and extracted with aqueous Na_2CO_3. The water phase was treated with 1M HCl and extracted with DCM. The organic phase was dried and concentrated under reduced pressure. The (*S*)-(+)-*O*-benzoyllactic acid was obtained in 30% yield.

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