Pergamon

Tetrahedron Letters 40 (1999) 6281–6284

TETRAHEDRON LETTERS

Enzymatic resolution of secondary alcohols coupled with ruthenium-catalyzed racemization without hydrogen mediator

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Received 24 May 1999; revised 16 June 1999; accepted 18 June 1999

Abstract

(η^5-Indenyl)RuCl(PPh_3)$_2$ was found to catalyze the racemization of secondary alcohols in the presence of triethylamine and oxygen. Unlike previously reported metal-catalyzed racemizations, ketones were not required as hydrogen mediators in our process. The Ru-catalyzed racemization was coupled with enzymatic acetylation for the dynamic kinetic resolution of secondary alcohols to give chiral acetates in good yields (60–98%) with high enantioselectivities (82–99% *ee*).

Dynamic kinetic resolution (DKR) is attracting much attention as a valuable method to overcome the fundamental limitation of conventional resolution of racemic compounds in the yield of desired isomers.[1] In DKR complete conversion to one isomer is possible by continuous isomerization of substrates during the resolution process. DKR has been applied to the substrates that are prone to in situ racemization.[2] In recent years transition metal-catalyzed racemization reactions have been coupled with enzymatic resolution for the DKR of secondary alcohols or allyl acetates.[3] In particular, Bäckvall et al. have reported an efficient procedure using a dimeric Ru(II) complex and a thermally stable lipase for DKR of secondary alcohols at 70°C.[3d] The metal-catalyzed racemization proceeds through a transfer hydrogenation process. Thus, ketones are required as hydrogen mediators for the racemization, which is an obvious problem needing to be resolved.[4]

We previously reported a highly efficient ruthenium catalyst for the racemization of secondary alcohols in the presence of strong bases.[5] However, the coupling of the catalytic racemization with lipase-catalyzed acetylation for DKR was unsuccessful because the strong base caused the chemical acetylation of the alcohols. Now we have overcome the chemical acetylation problem by using a weak base such as triethylamine, and herein describe a novel DKR system, in which hydrogen mediator is not required, for secondary alcohols (Scheme 1).

The racemization of (*S*)-1-phenylethanol (>99% *ee*) was investigated with varying reaction conditions (Table 1). In contrast to the racemization with a strong base such as KOH, a catalytic amount of

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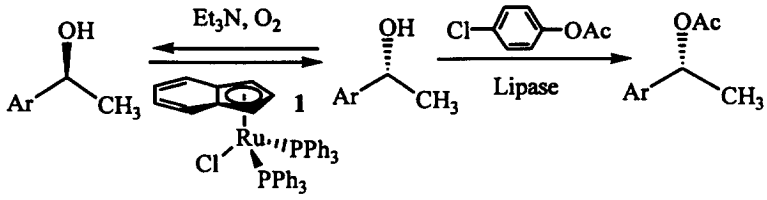
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01237-X



Scheme 1. Dynamic kinetic resolution of a secondary alcohol

Table 1
Racemization of (*S*)-1-phenylethanol with **1**[a]

entry	oxidant[b]	base[c]	solvent[d]	temp (°C)	time	% *ee*[e]
1	O_2	Et_3N	CH_2Cl_2	18	5 h	93
2	O_2	Et_3N	CH_2Cl_2	40	5 h	37
3	O_2	Et_3N	CH_2Cl_2	60	5 h	18
4	Me_3NO	Et_3N	CH_2Cl_2	40	5 h	56
5	O_2	$EtiPr_2N$	CH_2Cl_2	40	5 h	59
6	O_2	Me_3N	CH_2Cl_2	40	5 h	87
7	O_2	Et_3N	C_6H_6	40	5 h	63
8	O_2	Et_3N	$ClCH_2CH_2Cl$	40	5 h	67
9	O_2	Et_3N	THF	40	5 h	99
10	O_2	Et_3N	CH_2Cl_2, acetophenone[f]	40	5 h	44

[a] (*S*)-1-Phenylethanol of >99% *ee* and 2.0 mol% of **1** were used. [b] Oxygen (2 mol%) was injected after degassing the reaction mixture and filling the reaction flask with argon. [c] 3 equiv. [d] 0.17 M concentration. [e] Measured by HPLC equipped with a chiral column (Chiralcel OD®). [f] 1.0 equiv.

oxygen was necessary for the racemization with amine bases. Excess oxygen, however, decomposed the ruthenium complex **1** to unidentified species.[6] Trimethylamine *N*-oxide was also effective for the racemization (entry 4), but acetophenone was produced in a small amount (<2%). Under these conditions triphenylphosphine oxide was always formed as a byproduct. This observation suggests that oxygen and trimethylamine *N*-oxide acted as activators removing a phosphine ligand from the ruthenium center. *N*,*N*-Diisopropylethylamine and trimethylamine were less effective than triethylamine (entries 5 and 6). Trimethylamine appeared to react with dichloromethane to form (chloromethyl)trimethylammonium chloride. Dichloromethane was a better medium than benzene or 1,2-dichloroethane (entries 7 and 8). It is notable that the racemization was inhibited in tetrahydrofuran (entry 9) or by acetophenone (entry 10). Raising reaction temperature accelerated the racemization (entries 1–3).

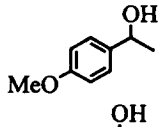
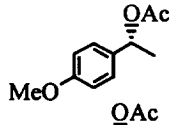
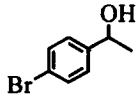
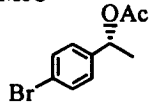
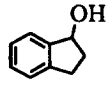
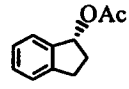
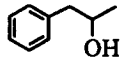
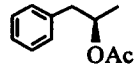
Enzymatic acetylation of racemic 1-phenylethanol was coupled with Ru-catalyzed racemization (Table 2). For the enzymatic resolution, *Pseudomonas cepacia* lipase (PCL) was employed,[7] and two alkenyl acetates and 4-chlorophenyl acetate were tested as acyl donors. Although acetophenone was not observed, 1-phenylethyl acetate was produced in less than 70% yield with low optical purity from the reactions using vinyl acetate and isopropenyl acetate (entries 1 and 2). The use of 4-chlorophenyl acetate led to significant improvement in the yield and the optical purity (entries 3–5). The best result (85%, 96% *ee*) was obtained at 60°C (entry 4).[8] When 5 mol% of trimethylamine *N*-oxide was used, the result was similar to that of entry 3 except the production of acetophenone in 3% (entry 5). Substitution of benzene for dichloromethane deteriorated the optical purity considerably (entry 6).

Table 2
Dynamic kinetic resolution of 1-phenylethanol[a]

entry	acyl donor[b]	oxidant[c]	solvent[d]	temp (°C)	% yield[e]	% *ee*[f]
1	vinyl acetate	O_2	CH_2Cl_2	40	61	65
2	isopropenyl acetate	O_2	CH_2Cl_2	40	67	85
3	*p*-chlorophenyl acetate	O_2	CH_2Cl_2	40	83	91
4	*p*-chlorophenyl acetate	O_2	CH_2Cl_2	60	85	96
5	*p*-chlorophenyl acetate	Me_3NO	CH_2Cl_2	40	82	90
6	*p*-chlorophenyl acetate	O_2	C_6H_6	40	81	68

[a] The reactions were performed on a 0.25 mmol scale with 5 mol% of the complex 1, 3 equiv of triethylamine, and 40 mg of PCL for 43 h. [b] 3 equiv. [c] 5 mol%. [d] 0.13 M concentration. [e] Yields were calculated from ^{1}H NMR spectra. [f] Measured by HPLC equipped with a chiral column purchased from Merck ((R,R) Whelk-01®).

Table 3
Dynamic kinetic resolution of secondary alcohols[a]

entry	substrate	product	% yield[b]	% *ee*[c]
1			82	99
2			98	99
3			88[d]	82[d]
4			60[e]	97

[a] The reactions were performed on a 0.25 mmol scale in 2.0 mL of CH_2Cl_2 with 5 mol% of 1, 5 mol% of O_2, 3 equiv of triethylamine, 3 equiv of *p*-chlorophenyl acetate, and 40 mg of PCL at 60 °C for 43 h. [b] Yields were calculated from ^{1}H NMR spectra. [c] Measured by HPLC equipped with a chiral column purchased from Merck ((R,R) Whelk-01®). [d] 15 mg of PCL was used. [e] (*S*)-1-Phenylpropan-2-ol was left as the major isomer in 76% *ee*.

The condition of entry 4 in Table 2 was adapted for DKR of four other secondary alcohols (Table 3). In comparison with 1-phenylethanol the derivatives having a *para*-substituent on the phenyl group were converted more selectively to the corresponding (*R*)-acetates regardless of the electronic property of the substituent (entries 1 and 2).[9] Acetylation of indanol was faster than others, but lower in selectivity (entry 3). Reducing the amount of PCL could enhance the selectivity. In DKR of 1-phenylpropan-2-ol having the hydroxy group at other than benzylic position, only 60% conversion was observed in 43 h while the optical purity was high (97% *ee*).

In summary, secondary alcohols were racemized by a ruthenium(II) complex with concurrent enzymatic acetylation of the alcohols. The ruthenium complex was activated by oxygen, and the racemization proceeded with weak bases. Under this condition alcohols were transformed enantioselectively to the corresponding acetates without chemical acetylation. Unlike previously reported metal-catalyzed DKR,

our procedure does not require ketones as hydrogen mediators. Further mechanistic studies are in progress to explain the distinctive features.

Acknowledgements

We gratefully acknowledge the financial support by the Basic Science Research Institute in POSTECH and the Center for Biofunctional Molecules.

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4. In Ref. 3d, DKR was carried out without adding ketones. However, substrate alcohols were oxidized to ketones through unidentified hydrogen-consuming processes.
5. Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545–5548.
6. When the reaction mixture was exposed to excess oxygen, the reaction mixture turned into a dark brown solution, losing the catalytic activity for racemization.
7. PCL immobilized on ceramic particles (trade name: Lipase PS-C (type II), Amano, Japan) was used.
8. DKR of (4-bromophenyl)ethanol: In a 50 mL flask equipped with a grease-free high-vacuum stopcock (4-bromophenyl)ethanol (201 mg, 1.00 mmol), (η^5-indenyl)RuCl(PPh_3)$_2$ (38.8 mg, 0.0500 mmol), Et_3N (420 μL, 3.00 mmol), 4-chlorophenyl acetate (510 mg, 2.99 mmol), and PCL (160 mg) were mixed in CH_2Cl_2 (8.0 mL). The resulting red-brown suspension was degassed with sonication under vacuum, and the flask was filled with argon. Oxygen (1.12 mL, 0.0500 mmol) was injected to the suspension, which was heated at 60°C for 43 h. The reaction mixture was filtered and separated on silica gel (ethyl acetate:hexane, 1:8) to give a mixture (481 mg) of (4-bromophenyl)ethyl acetate (93%, 99% *ee*) and 4-chlorophenyl acetate (1.00:1.61 ratio by ^{1}H NMR).
9. The absolute configuration of the acetates was determined by comparing their optical rotations with known data. See: (a) Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285–3294. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 598–600.