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Catalytic Asymmetric Hydrolysis: Asymmetric Hydrolytic Protonation of Enol Esters Catalyzed by Phase-Transfer Catalysts

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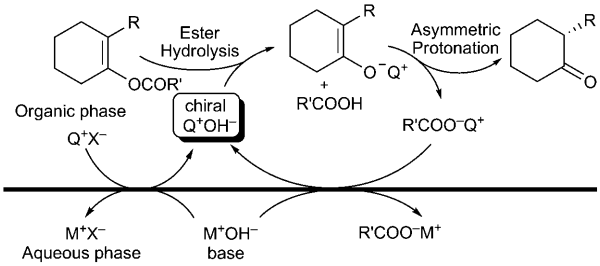
Hydrolase-catalyzed stereoselective ester hydrolysis is one of the most important and fundamental reactions in fine chemical productions.[1] However, the reaction with artificial catalysts[2] has still not been attained even though enzymatic reactions have many drawbacks.[3] In this context, we have investigated the development and expansion of the substrate scope of transition-metal-catalyzed asymmetric hydrolysis and alcoholysis, but the asymmetric hydrolysis of unactivated carboxylic esters remains undeveloped.[4] The difficulties of ester hydrolysis probably arise from the low reactivity with acid catalysts. In contrast, base hydrolysis of esters proceeds smoothly with water under homogeneous conditions even at low temperature. Accordingly, asymmetric hydrolysis of esters is expected to be achieved by using chiral phase-transfer catalysts (PTC) to catalytically generate a chiral ammonium hydroxide salt (Q^+OH^-) although asymmetric reactions with Q^+OH^- as a chiral hydroxide nucleophile have yet to be reported.[5] Based on our investigation, we envisioned hydrolytic asymmetric protonation of enol esters, which is one of the important hydrolase-catalyzed asymmetric hydrolysis reactions and also has been hitherto conducted only by hydrolases[1c,6,7] (Scheme 1). Herein, we report the first synthetically useful asymmetric hydrolysis of enol esters with artificial phase-transfer catalysts. In the preliminary studies, several kinds of esters such as aryl esters, β-lactones, and activated α,α-disubstituted esters were found to be hydrolyzed by phase-transfer catalytic conditions.



Scheme 1. Working hypothesis of catalytic asymmetric hydrolytic protonation of enol esters.

In particular, enol esters derived from 2-substituted ketones gave α-tertiary alkyl ketones with good enantioselectivities. Therefore, further investigations of the reaction were performed. A simple acetyl enolate derived from 2-propylcyclohexanone (**2a**) were sluggish and the enantioselectivity gradually decreased during the reaction (with an enantiomer ratio (e.r.) of up to 79:21 with **2a**; see the Supporting Information). A faster reaction was observed with a chloroacetyl enolate (**2c**). In this case, the reaction proceeded and gave the desired product with a moderate e.r. (30% yield, 85:15 e.r., Table 1, entry 1). The addition of small amount of alcohol had a good effect on the yield and enantioselectivity; the best results were achieved with 2-chloroethanol (Table 1, entries 2–4; for details, see the Supporting Information).

Next, the optimum solvent system was surveyed and mesitylene/$CHCl_3$ (1:2) was found to be the best system (Table 1, entry 5). Reducing the amount of alcohol to 0.5 equiv showed no effect on the enantioselectivity (Table 1, entry 5 vs. entry 6). Although roles of the alcohol are still obscure, promoting mass transfer of PTC between phases seems plausible since addition of a surfactant (Triton X-100, 5 mol%) as an alternative of 2-chloroethanol also gave a similar selectivity (Table 1, entry 11). In an investigation of catalysts, catalyst **1a**, which has anthracenylmethyl group developed by Lygo et al.[8] and Corey et al.[9], was found to be the best performance in the asymmetric hydrolysis of enol esters; the functional group at the 9-position was shown to have a significant effect on the enantioselectivities (Table 1, entries 5 and 7–10). Catalyst loading of **1a** can be lowered to 2 mol% with a slight loss of enantioselectivity. This reaction was also carried out on a gram scale and gave virtually the same result (Table 1, entry 12). Under the conditions of further lower catalyst loadings (0.5 and 0.1 mol%), good yields (99 and 78%) and slightly lower enantiomeric ratios (90:10 and 87:13) were obtained (Table 1, entries 13 and 14). In these entries, concentrated conditions (substrate concentration of 14%) and lower amounts of additive alcohols (10 mol%) were employed. It is noteworthy that the reported enzymatic reaction with an enol acetate of 2-propylcyclohexanone catalyzed by a yeast, *Pichia miso* IAM 4682, could not be tolerated under concentrated conditions (substrate conc = 0.2%, 80% yield, 9:91

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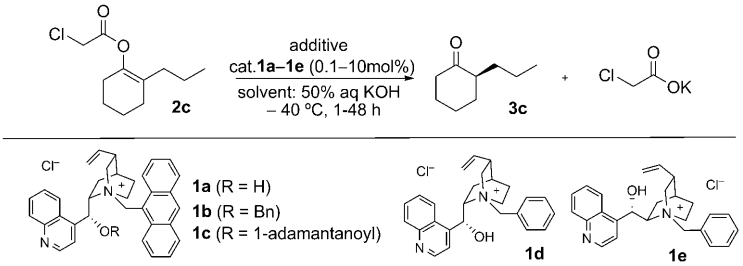
Table 1. Asymmetric hydrolysis of enol esters catalyzed by PTC.

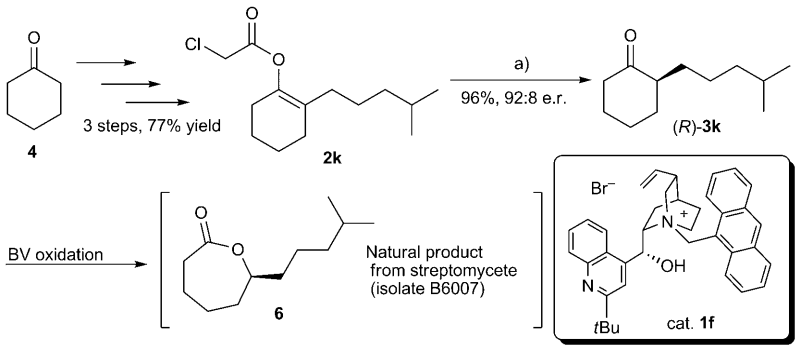


Entry	cat. [(mol %)]	*t* [h]	Additive [(equiv)]	Solvent	Yield[a] [%]	e.r.
1[b]	**1a** (10)	1	none	$CHCl_3$	30	85:15
2[b]	**1a** (10)	1	ethanol (1.0)	$CHCl_3$	66	87:13
3[b]	**1a** (10)	1	2,2,2-trifluoroethanol (1.0)	$CHCl_3$	73	89:11
4[b]	**1a** (10)	1	2-chloroethanol (1.0)	$CHCl_3$	67	90:10
5[b]	**1a** (10)	1	2-chloroethanol (1.0)	mesitylene:$CHCl_3$ (1:2)	64	92:8
6[c]	**1a** (10)	12	2-chloroethanol (0.5)	mesitylene:$CHCl_3$ (1:2)	98	92:8
7[b]	**1b** (10)	1	2-chloroethanol (1.0)	mesitylene:$CHCl_3$ (1:2)	28	48:52
8[b]	**1c** (10)	1	2-chloroethanol (1.0)	mesitylene:$CHCl_3$ (1:2)	57	89:11
9[b]	**1d** (10)	1	2-chloroethanol (1.0)	mesitylene:$CHCl_3$ (1:2)	87	88:12
10[b]	**1e** (10)	1	2-chloroethanol (1.0)	mesitylene:$CHCl_3$ (1:2)	75	66:34
11[c]	**1a** (10)	1	Triton-X100 (0.05)	mesitylene:$CHCl_3$ (1:2)	65	91:9
12[b,d]	**1a** (2)	24	2-chloroethanol (0.5)	mesitylene:$CHCl_3$ (1:2)	96	91:9
13[e]	**1a** (0.5)	24	2-chloroethanol (0.1)	mesitylene:$CHCl_3$ (1:2)	99	90:10
14[f]	**1a** (0.1)	48	2-chloroethanol (0.1)	mesitylene:$CHCl_3$ (1:2)	78	87:13

[a] GC yield. [b] 0.1 mmol scale, organic solvents (400 μL), 50% aq KOH (200 μL). [c] 0.1 mmol scale, organic solvents (400 μL), 50% aq KOH (100 μL). [d] 5 mmol scale (approx 1 g), organic solvents (20 mL), 50% aq KOH (5 mL). [e] 1 mmol scale, organic solvents (1 mL), 50% aq KOH (0.5 mL). [f] 2 mmol scale, organic solvents (2 mL), 50% aq KOH (1 mL).

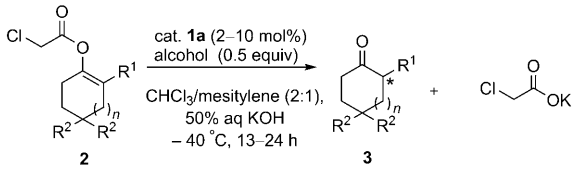
e.r.; substrate conc = 1.0%, 84% yield, 16:84 e.r.).[6c] In addition, the reactions with 2–0.1 mol% of catalyst loadings are rather low and rare in the field of asymmetric organocatalysis. With the optimized catalyst in hand, the substrate scope of the reaction was investigated using a series of enol esters derived from 2-substituted cyclic ketones. The substrates derived from cyclohexanones and cycloheptanones having simple alkyl groups were efficiently transformed into the corresponding 2-substituted cyclic ketones in excellent yields and with high enantioselectivities (Table 2). When comparing the 10 and 2 mol% conditions for three substrates, the former conditions gave a slightly better e.r. in every case (Table 2, entries 2–7), therefore the 10 mol% conditions were used for the other substrates. Among them, an e.r. of 95:5 was observed with 3 substrates. As an application of this reaction, we conducted a formal total synthesis of (*R*)-10-methyl-6-undecanolide (**6**), which is a biologically active natural product isolated from a marine streptomycete (isolate B6007, Scheme 2).[10] In case of the substrate **2k**, the asymmetric hydrolysis with catalyst **1a** afforded (*R*)-2-(4-methylpentyl)cyclohexanone (**3k**) with an e.r. of 89:11. Further catalyst screening disclosed that the reaction with catalyst **1f** gave **3k** in excellent yield and with a higher e.r. (Scheme 2, 96%, 92:8 e.r.). The desired lactone was obtained from **3k** by a Baeyer–Villiger oxidation in 90% yield in the literature.[11] A previous asymmetric synthesis of (*R*)-**3k** was performed through 6 steps with rather expensive and explosive reagents. Our method is advantageous in terms of a shorter synthetic route, a simpler and safer method, and better total yield from a commercially available inexpensive starting material.

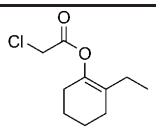
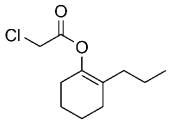
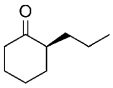
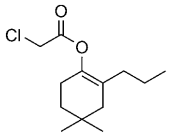
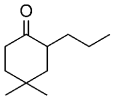
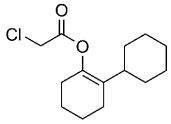
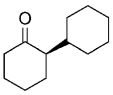
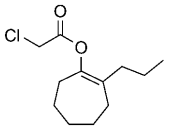
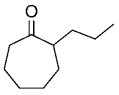
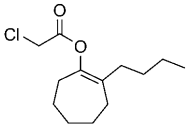
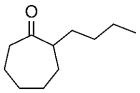
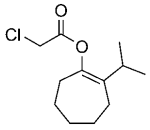
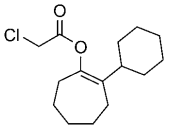
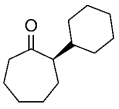
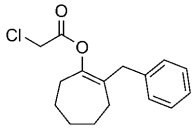
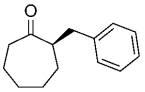
With respect to the structure of the catalyst, there is a possibility that the hydroxy group of catalyst **1a** may react with primary alkyl halides such as 2-chloroethanol, substrate, or chloroacetic acid to give other catalytic species. Indeed, the alkylation of hydroxyl group of the catalyst was already reported in the field of the PTC catalyzed asymmetric alkylation.[12] Thus, the mass balance of the reaction was confirmed and it was revealed that 99% of the product ketone, 99% of chloroacetic acid, and 88% of 2-chloroethanol existed in the reaction mixture (for details, see the Supporting Information). Alkylation of the catalyst is not likely because the other alcohols (that do not act as alkylating agents) and the surfactant brought a similar effect to 2-choroethanol although the alkylation cannot be excluded completely. Therefore, it is reasonable that the structure of the cation part of the catalyst remains intact. A stoichiometric reaction was carried out in the presence of the in situ



Scheme 2. Application for the synthesis of a biologically active cyclic lactone. a) Reaction conditions; catalyst **1f** (10 mol%), 2-chloroethanol (0.5 equiv), and $CHCl_3$/mesitylene (2:1) at −40°C for 13 h. BV = Baeyer–Villiger.

Table 2. Substrate scope for the asymmetric hydrolysis of enol ester.[a]

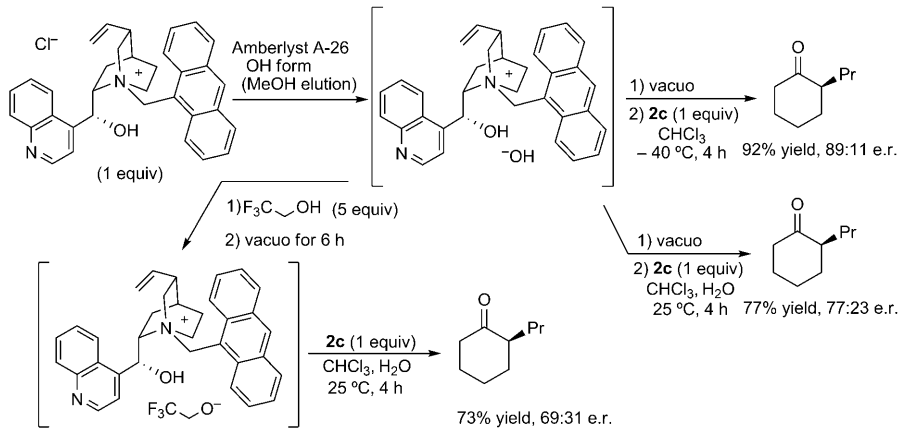


Entry	Substrate		Product		Yield[a] [%]	e.r. (config)
1		**2b**		**3b**	98[b]	87:13 (*S*)
2		**2c**		**3c**	96[c,d]	92:8 (*S*)
3					96[d,e,f]	91:9 (*S*)
4		**2d**		**3d**	99[d]	92:8 (+)
5					96[d,e]	92:8 (+)
6		**2e**		**3e**	94[d]	87:13 (*R*)
7					93[d,e]	86:14 (*R*)
8		**2f**		**3f**	91[d]	95:5[g] (+)
9		**2g**		**3g**	91[d]	95:5[g] (+)
10		**2h**		**3h**	97[d]	95:5[h] (+)
11		**2i**		**3i**	96[d]	94:6 (*R*)
12		**2j**		**3j**	99[d]	89:11 (*R*)

[a] Reactions were carried out on 0.1 mmol scale with 10 mol% of the catalyst unless otherwise noted. [b] GC yield. [c] 1 mmol scale. [d] Yield of the isolated product. [e] 24 h, 2 mol% of the catalyst was used. [f] 5 mmol scale. [g] Enantiomer ratios of products were analyzed by ^{1}H NMR spectroscopy after ketones were reduced and esterified to the corresponding Mosher's esters. [h] The enantiomer ratio of product was analyzed by chiral GC after ketones were reduced to the corresponding alcohol.

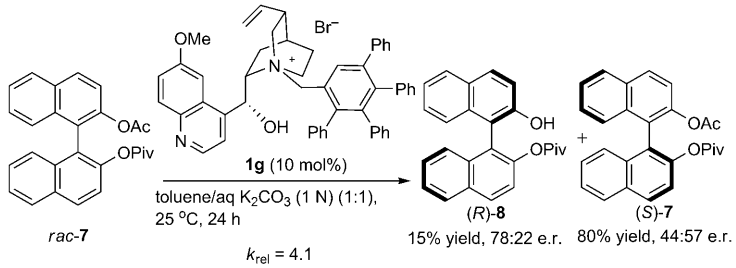
generated Q^+OH^- ion pair[13] to assess the involvement of Q^+OH^- as an active species in the reaction, which afforded the desired product in 92% yield and with an e.r. of 89:11 (Scheme 3). The absolute structure of the product coincided with the product of the catalytic reaction. Additionally, stoichiometric reactions using the chiral ammonium 2,2,2- trifluoroethoxide ($Q^+CF_3CH_2O^-$) and Q^+OH^- in the presence of water were performed. As a result, the reaction with Q^+OH^- gave the product with a higher e.r. than that with $Q^+CF_3CH_2O^-$ (Scheme 3, 77:23 vs. 69:31). These results indicate that Q^+OH^- is the active species of asymmetric hydrolysis. To obtain the insights of the structure of the active species, we performed NMR experiments of $Q^+CF_3CH_2O^-$ as an analogue of Q^+OH^-.

An interionic NOE between the 2,2,2-trifluoroethanoxide protons and the quinoline proton located proximal to the 9-hydroxyl group was observed (For detail, see the Supporting Information). Additionally, given all the obtained NOEs, the alkoxide anion is likely located near hydroxy group of the ammonium cation. Furthermore, it was reported that the BH_4^- anion of the *N*-9-anthracenylmethyl cinchonidinium tetrahydroborate salt prefers to be located near the 9-hydroxy group.[14] These facts suggest that OH^- is located near the 9-hydroxy group of the ammonium cation. In terms of the reaction mechanism, this asymmetric hydrolysis is composed of hydrolysis followed by protonation. Although the first hydrolysis step can affect the enantioselectivity of next protonation step, the result of stoichiometric reaction of the ammonium alkoxide indicated that the enantioselectivity mainly originated from the protonation step. Additionally, the stoichiometric reactions suggested that the contact ion pair of the unstable enolate and the ammonium cation was generated in the organic phase after the hydrolysis of the substrate. It is different from the PTC-catalyzed asymmetric alkylation which generates contact ion pair of a stable enolate and an ammonium cation by the anion exchange with

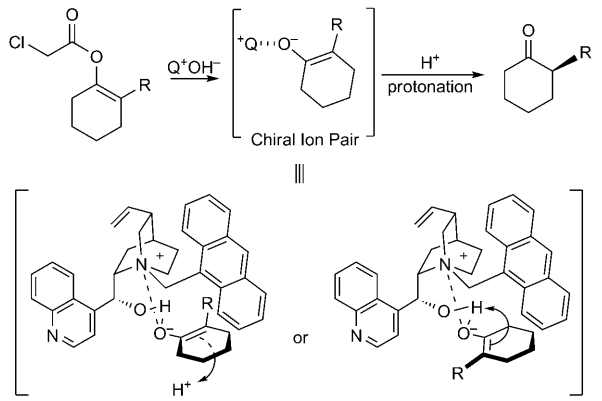


Scheme 3. In situ generated Q^+OR^- as a stoichiometric reagent of asymmetric hydrolysis.

metal enolates.[15] The mechanism of enantioface differentiating protonation may be similar to those of PTC-catalyzed asymmetric aldol reactions.[5a] From the structural insights of active species, the enantioselective protonation of an enolate likely occurs near the 9-hydroxy group of the catalysts. We speculate that the hydroxy group of the catalyst interacts with reaction intermediates through hydrogen bonding (Scheme 4). In this reaction, it is still obscure whether a well-organized chiral hydroxide species was generated or not because enantioselective step of asymmetric hydrolysis of the enol ester is not the nucleophilic attack of hydroxide but in the protonation of the enolate. However, the fact that asymmetric induction was also observed in the case of hydrolytic kinetic resolution of an acetate ester derived from 2,2′-dihydroxybinaphthyl is indirect evidence for the generation of a well-organized chiral hydroxide (Scheme 5, $k_{rel}=4.1$).



Scheme 5. Kinetic resolution of an acetate ester with a binaphthyl backbone.



Scheme 4. A possible reaction mechanism for the asymmetric hydrolysis of enol esters.

In conclusion, we have achieved the first non-biomimetic asymmetric hydrolysis of esters catalyzed by artificial molecular catalysts with high catalytic efficiency in buffer-free conditions. Enzymatic reactions follow Michaelis–Menten kinetics because of the tight substrate binding characteristic of enzymes, which means the reaction rate enhancement by raising the concentration of substrates is highly limited. On the other hand, artificial catalysts often show collision-type kinetics. Therefore, reactions catalyzed by artificial molecular catalysts are free from that limitation. Non-enzymatic catalytic reactions have a considerable potential to replace industrially used enzymatic reactions. The well-organized chiral ammonium hydroxide species will give researchers numerous opportunities to develop new asymmetric reactions with water, which have been performed only by hydrolases in the past. Further mechanistic study, extension of the reaction scope, and development of more efficient catalytic systems are currently underway in our laboratory.

Experimental Section

Typical Procedures of asymmetric hydrolysis of enol esters (Table 2, entry 3): *N*-9-anthracenylmethyl cinchonidinium chloride (61 mg, 0.1 mmol, 2 mol %) was added to the $CHCl_3$/mesitylene (2:1, 20 mL) solution followed by the addition of 2-chloroethanol (67 μL, 0.5 mmol, 0.1 equiv) and 50 % aq KOH (5 mL). Then, the mixture was stirred for 10 min at −40 °C followed by the addition of enol ester **2c** (1.08 g, 5 mmol, 1 equiv). The reaction mixture was stirred for 24 h at −40 °C. Then, the reaction mixture was immediately passed through a thin pad of silica gel and the resultant crude product was purified by silica gel column chromatography to give (*R*)-**3c** (673 mg, 4.80 mmol, 96 %, 91:9 e.r.).

Acknowledgements

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Keywords: alkaloids · asymmetric protonation · enol esters · hydrolysis · phase-transfer catalysts

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