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出版情報：Chemistry : A European Journal. 17 (26), pp.7178-7182, 2011-05-12. WILEY-VCH Verlag
バージョン：
権利関係：

CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Catalytic Asymmetric Hydrolysis: Asymmetric Hydrolytic Protonation of Enolesters Catalyzed by Phase Transfer Catalysts

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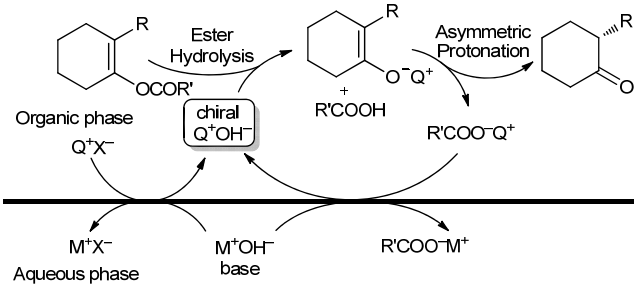
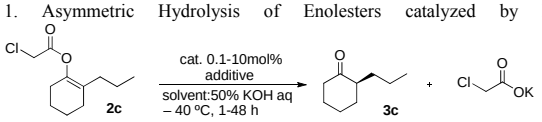
Hydrolase-catalyzed stereoselective ester hydrolysis is one of the most important and fundamental reactions in fine chemical productions.[1] However, the reaction with artificial catalysts[2] still has not been attained though enzymatic reactions have many drawbacks.[3] In this context, we have investigated to develop and expand the substrate scope of transition metal-catalyzed asymmetric hydrolysis and alcoholysis but asymmetric hydrolysis of unactivated carboxylic esters remained undeveloped.[4] The difficulties of ester hydrolysis probably arise from the low reactivity against 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) in order to catalytically generate a chiral ammonium hydroxide salt (Q^+OH^-) although asymmetric reactions with Q^+OH^- as a chiral hydroxide nucleophile have never been reported yet.[5] Base on our investigation, we envisioned hydrolytic asymmetric protonation of enolesters, 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 enolesters with artificial phase transfer catalysts. In the preliminary studies, several kinds of esters such as arylesters, β-lactones and activated α,α-disubstituted esters were found to be hydrolyzed by phase transfer catalytic condition.



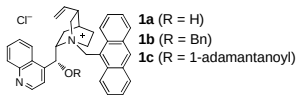
Scheme 1. Working Hypothesis of Catalytic Asymmetric Hydrolytic Protonation of Enolesters

Table 1. Asymmetric Hydrolysis of Enolesters catalyzed by PTC

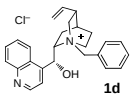


entry	cat. (mol%)	time (h)	additive (eq)	solvent	yield[a](%)	er
1[b]	**1a** (10)	1	none	$CHCl_3$	30	85:15
2[b]	**1a** (10)	1	ethanol (1)	$CHCl_3$	66	87:13
3[b]	**1a** (10)	1	2,2,2-trifluoroethanol (1)	$CHCl_3$	73	89:11
4[b]	**1a** (10)	1	2-chloroethanol (1)	$CHCl_3$	67	90:10
5[b]	**1a** (10)	1	2-chloroethanol (1)	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)	Mesitylene: $CHCl_3$ = 1:2	28	48:52
8[b]	**1c** (10)	1	2-chloroethanol (1)	Mesitylene: $CHCl_3$ = 1:2	57	89:11
9[b]	**1d** (10)	1	2-chloroethanol (1)	Mesitylene: $CHCl_3$ = 1:2	87	88:12
10[b]	**1e** (10)	1	2-chloroethanol (1)	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

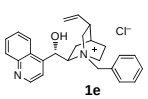
[a] GC yield, [b] 0.1 mmol scale, organic solvents (400 μL), 50% KOH aq (200 μL). [c] 0.1 mmol scale, organic solvents (400 μL), 50% KOH aq (100 μL). [d] 5 mmol scale (ca. 1 g), organic solvents (20 mL), 50% KOH aq (5 mL). [e] 1 mmol scale, organic solvents (1 mL), 50% KOH aq (0.5 mL). [f] 2 mmol scale,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



1a (R = H)
1b (R = Bn)
1c (R = 1-adamantanoyl)



1d



1e

Especially, enolesters derived from 2-substituted ketones gave α-tertiary alkyl ketones in 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 (up to 79:21 er with **2a**. See Supproting Information.). A faster reaction was observed with a chloroacethyl enolate (**2c**). In this case, the reaction proceeded and gave the desired product in moderate er (30% yield, 85:15 enantiomer ratio (er), Table 1, entry 1). The addition of small amount of alcohols had a good effect on the yield and enantioselectivity. Especially, 2-chloroethanol gave the best results (Table 1, entries 2-4, For detail, see Supporting Information.).

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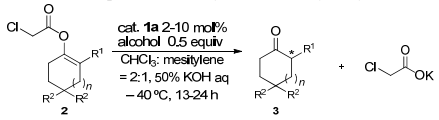
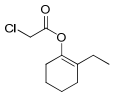
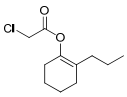
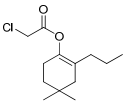
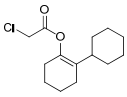
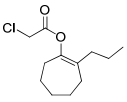
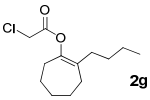
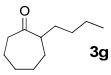
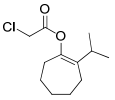
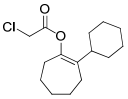
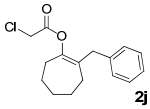
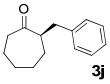
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

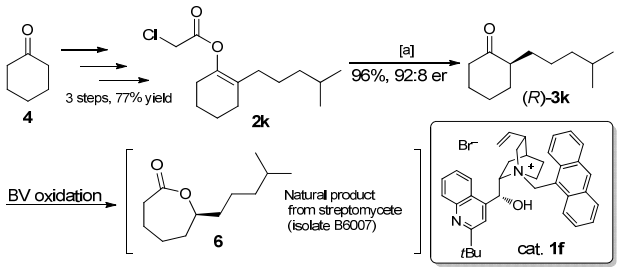
Table 2. Substrate Scopes for Asymmetric Hydrolysis of Enolester[a]



entry	substrate	product	yield (%)	er (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] Isolated yield, [e] 24 h, 2 mol% of the catalyst was used. [f] 5 mmol scale, [g] Enantiomer ratios of products was analyzed by ^{1}H NMR after ketones were reduced and esterified to the corresponding Mosher's esters. [h] The enanitomer ratio of product was analyzed by chiral GC after ketones were reduced to the corresponding alcohol.

Next, the optimum solvent system was surveyed, and mesitylene-$CHCl_3$ (volume ratio = 1:2) was found as the best one (Table 1, entry 5). Reducing the amount of alcohols 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-X100, 5 mol%) as an alternative of 2-chloroethanol also gave a similar selectivity (Table 1, entry 11). Based on the investigation of catalysts, **1a** which has anthracenylmethyl group developed by Lygo et al.[8] and Corey et al.[9] found to be the best performance in the asymmetric hydrolysis of enolesters, and the functional group at the 9-position had a significant effect on the enantioselectivities (Table 1, entries 5, 7-10). Catalyst loadings of **1a** could be reduced to 2 mol% with a little loss of enantioselectivity. This reaction was also carried out in 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 ers (90:10 and 87:13) were obtained (Table 1, entries 13 and 14). In these entries, concentrated conditions (substrate concentration = 14%) and lower amounts of additive alcohols (10 mol%) were employed. It is noteworthy that the reported enzymatic reaction with an enolacetate of 2-propylcyclohexanone catalyzed by a yeast, *Pichia miso* IAM 4682, could not be tolerant under

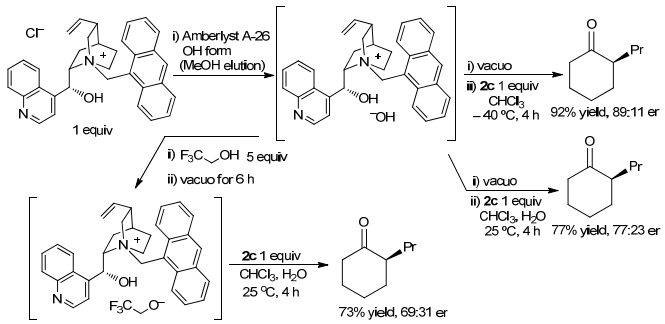


[a] Reaction condition; catalyst **1f** 10 mol%, 2-chloroethanol 0.5 eq., $CHCl_3$/mesythylene = 2:1, – 40 °C, 13 h.

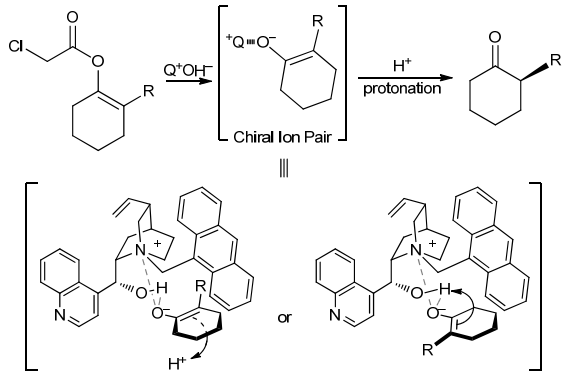
Scheme 3. Application for the Synthesis of a Biologically Active Cyclic Lactone

concentrated conditions (substrate conc. = 0.2%, 80% yield, 9:91 er, substrate conc. 1.0%, 84% yield, 16:84 er).[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 enolesters 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 high enantioselectivities (Table 2). When comparing the 10 and 2 mol% conditions for 3 substrates, the former condition gave slightly better ers in every cases (Table 2, entries 2-7), therefore the 10 mol% condition was used for other substrates. Among them, the er 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).[10] In case of the substrate **2k**, the asymmetric hydrolysis with catalyst **1a** afforded (*R*)-2-(4-methylpentyl)cyclohexanone (**3k**) in 89:11 er. Further catalyst screening disclosed that the reaction with catalyst **1f** gave **3k** in excellent yield and higher er (Scheme 3, 96%, 92:8 er). The desired lactone was obtained from **3k** by Baeyer-Villiger oxidation in 90% yield in literature. A previous asymmetric synthesis of (*R*)-**3k** was performed through 6 steps with rather expensive and explosive reagents.[11] 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.

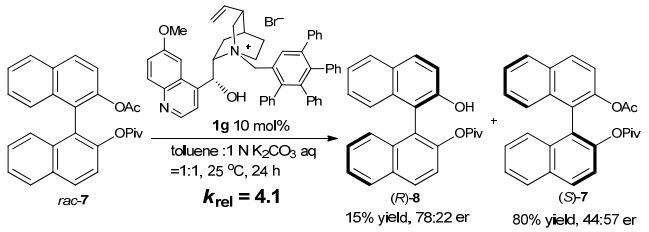
With respect to the structure of the catalyst, there is a possibility that the hydroxy group of catalyst **1a** may react with primary alkyl halide such as 2-chloroethanol, substrate or chloroacetic acid to give other catalytic species. Indeed, the alkylation of hydroxyl group of the catalyst was already reported in the field of the PTC catalyzed asymmetric alkylation.[12] Thus, 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 detail, see Supporting Information). Alkylation of the catalyst is not likely because the other alcohols which does 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 generated Q^+OH^- ion pair[13] in order to assess the involvement of Q^+OH^- as an active species in the reaction, which afforded the desired product in 92% yield, 89:11 er (Scheme 4). The absolute structure of the product was 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 in higher er than that with $Q^+CF_3CH_2O^-$ (Scheme 4, 77:23 vs 69:31). These results indicate that Q^+OH^- is the active species of asymmetric hydrolysis. In order to obtain the insights of the structure of the active species, we performed NMR experiments of $Q^+CF_3CH_2O^-$ as an analog of Q^+OH^-. An



Scheme 4. In situ Generated Q^+OR^- as a Stoichiometric Reagent of Asymmetric Hydrolysis



Scheme 5. A Possible Reaction Mechanism of Asymmetric Hydrolysis of Enolesters



Scheme 6. Kinetic Resolution of an Acetate Ester Bearing Binaphthyl Backbone

interionic NOE between the 2,2,2-trifluoroethanoxide protons and the quinoline proton adjacent to the sp^2 nitrogen atom was observed (For detail, see 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 BH_4^- anion of the *N*-9-anthracenylmethyl cinchonidinium tetrahydroborate salt prefers to be located near the 9-hydroxy group in the literature.[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 and following protonation. Although the first hydrolysis step can affect the enanitioselectivity 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 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 5). 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 enolester 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 an indirect evidence for the generation of well-organized chiral hydroxide (Scheme 6, k_{rel} = 4.1).

In conclusion, we 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 overcome 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 enolesters (Table 2, entry 3) *N*-9-anthracenylmethyl cinchonidinium chloride (61 mg, 0.1 mmol, 2 mol%) was added to the $CHCl_3$/mesitylene (volume ratio = 2:1, 20 mL) solution followed by the addition of 2-chloroethanol (67 μL, 0.5 mmol, 0.1 equiv) and 50% KOH aq (5 mL). Then, the mixture was stirred for 10 min at – 40 °C followed by the addition of enolester **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 er).

Acknowledgements

This study was financially supported by a Grant-in-Aid for Global-COE pro-gram, "Science for Future Molecular Systems" and Scientific Research (A) (No. 20245014).

Keywords: asymmetric hydrolysis • asymmetric protonation • phase transfer catalysts • cinchona alkaloids • enolesters

[1] a) A. H. Kamaruddin, M. H. Uzir, H. Y. Aboul-enein, H. N. A. Halim, Chirality, **2009**, *21*, 449–467; b) E. Fogassy, M. Nógrádi, D. Kozma, G. Egri, E. Pálovics, V. Kiss, *Org. Biomol. Chem.* **2006**, *4*, 3011–3030; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kesseler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788 – 824; d) A. J. J. Straathof, S. Panke, *A.* Schmid, *Curr. Opin. Biotechnol.* **2002**, *13*, 548 – 556; e) H. Tye, *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 275–298; f) R. D. Schmid, R. Verger, *Angew. Chem. Int. Ed.* **1998**, *37*, 1608 – 1633.

[2] a) J. M. Brown, C. Bunton, A. *J. Chem. Soc., Chem. Commun.* **1974**, 969 – 971; b) K. Yamada, H. Shosenji, H. Ihara, *Chem. Lett.* **1979**, *5*, 491 – 494; c) H. Ihara, S. Ono, H. Shosenji, K. Yamada, *J. Org. Chem.* **1980**, *45*, 1623 – 1625; d) Y. Ihara, Y. Igata, Y. Okubo, M. Nango, *J. Chem. Soc., Chem. Commun*, **1989**, 1900 – 1902; e) M. C. Cleij, W. Drenth, R. J. Nolte, M. *J. Org. Chem.* **1991**, *56*, 3883 – 3891; f) J. G. J. Weijnen, A. Koudijs, J. F. J. Engbersen, *J. Org. Chem.* **1992**, *57*, 7258 – 7265; g) T. Kida, K. Kajihara, K. Isogawa, W. Zhang, Y. Nakatsuji, I. Ikeda, M. Akashi, *Langmuir*, **2004**, *20*, 8504 –8509; h) G. L. Trainor, R. Breslow, *J. Am. Chem. Soc.* **1981**, *103*, 154 – 158; i) R. Breslow, G. L. Trainor, A. Ueno, *J. Am. Chem. Soc.* **1983**, *105*, 2739 – 2744; j) R. Ueoka, Y. Matsumoto, R. A. Moss, S. Swarup, A. Sugii, K. Harada, J. Kikuchi, Y. Murakami, *J. Am. Chem. Soc.* **1988**, *110*, 1588 – 1595; k) M. Murakami, H. Itatani, K. Takahashi, J. Kang, K. Suzuki, *Mem. Inst. Sci. Ind. Res., Osaka Univ.* **1963**, *20*, 95 – 106; l) J. E., Jr. Hix, M. Jones, *J. Am. Chem. Soc.* **1968**, *90*, 1723 – 1783; m) R. R. Davies, M. D. Distefano, *J. Am. Chem. Soc.* **1997**, *119*, 11643 – 11652.

[3] a) A. S. Bommarius, B. L. Riebel, *Biocatalysis*, WILEY-VCH, Weinheim, **2004**, p. 1-8; b) J. Hagen, *Industrial catalysis: practical approach*, 2nd Edition, WILEY-VCH, Winheim, **2006**, p. 10.

[4] a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science*, **1997**, *277*, 936 – 938; b) H. Aoyama, M. Tokunaga, S. Hiraiwa, Y. Shirogane, Y.

Obora, Y. Tsuji, *Org. Lett.* **2004**, *6*, 509 – 512; c) H. Aoyama, M. Tokunaga, J. Kiyosu, T. Iwasawa, Y. Obora, Y. Tsuji, *J. Am. Chem. Soc.* **2005**, *127*, 10474 – 10475; d) T. Sakuma, E. Yamamoto, H. Aoyama, Y. Obora, Y. Tsuji, M. Tokunaga, *Tetrahedron*: *Asymmetry* **2008**, *19*, 1593 – 1599; e) H. Itoh, E. Yamamoto, S. Masaoka, K. Sakai, M. Tokunaga, *Adv. Synth. Catal.* **2009**, *351*, 1796 – 1800; f) A. Hamasaki, E. Yamamoto, H. Itoh, M. Tokunaga, *J. Organomet. Chem.* **2011**, *696*, 202 – 210.

[5] a) K. Maruoka, *Asymmetric Phase Transfer Catalysis*, (Eds: K. Maruoka), WILEY-VCH, Weinheim, **2008**; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656 –5682.

[6] For enzymatic asymmetric hydrolysis of enolesters see: a) T. Hirata, K. Shimoda, D. Ohba, N. Furuya, S. Izumi, *J. Mol. Catal. B*: *Enzymatic*, 1998, *5*, 143 – 147; b) K. Shimoda, N. Kubota, T. Hirata, T. Kawano, *J. Mol. Catal. B*: *Enzymatic*, **2004**, *29*, 123 – 127; c) K. Matsumoto, S. Tsutsumi, T. Ihori, H. Ohta, *J. Am. Chem. Soc.* **1990**, *112*, 9614 – 9619; d) H. Ohta, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2895 – 2911; e) P. Duhamel, P. Renouf, D. Cahard, A. Yebga, J. M. Poirier, *Tetrahedron Asymmetry*. **1993**, *4*, 2447 – 2450; f) K. Matsumoto, N. Suzuki, H. Ohta, *Tetrahedron Lett.* **1990**, *31*, 7163 – 7166; g) H. Ohta, K. Matsumoto, S. Tsutsumi, T. Ihori, *J. Chem. Soc., Chem. Commun.* **1989**, 485 – 486.

[7] Related asymmetric protonation reactions mainly employed silyl enol ethers which are not subject of biocatalysis.: a) M. Sugiura, T. Nakai, *Angew. Chem., Int. Ed.* **1997**, *36*, 2366 – 2368; b) A. Yanagisawa, T. Touge, T. Arai, *Angew. Chem., Int. Ed.* **2005**, *44*, 1546 – 1548; c) J. T. Mohr, T. Nishimata, D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 11348 – 11349; d) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem., Int. Ed.* **2007**, *46*, 7220 – 7223; e) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246 – 9247; f) M. Morita, L. Drouin, R. Motoki, Y. Kimura, I. Fujimori, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3858 – 3859; g) J. T. Mohr, A.Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359 – 369; h) D. Uraguchi, N. Kinoshita, T. Ooi, *J. Am. Chem. Soc.* **2010**, *132*, 12240 – 12242; i) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 2860 – 2861; j) C. H. Cheon, T. Imahori, H. Yamamoto, *Chem. Commun.* **2010**, *46*, 6980 – 6982.

[8] B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595 – 8598.

[9] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414 – 12415.

[10] K. Striyzke, S. Schulz, H. Laatsch, E. Helmke, W. Beil, *J. Nat. Prod.* **2004**, 67, 395 – 401.

[11] (a) D. Soorukram, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 3686 – 3689; (b) E. Hupe, P. Knochel, *Org. Lett.* **2003**, *5*, 1059 – 1061.

[12] B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518 – 525.

[13] A. Ando, T. Miura, T. Tatematsu, T. Shioiri, *Tetrahedron Lett.* **1993**, *34*, 1507 – 1510.; Intramolecular zwitterionic and bihydroxide structures cannnot be excluded.

[14] C. Hofstetter, P. S. Wilkinson, T. C. Pochapsky, *J. Org. Chem.* **1999**, *64*, 8794 – 8800.

[15] S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi, K. Maruoka, *Angew. Chem., Int. Ed.* **2005**, *44*, 625 – 628.

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Revised: ((will be filled in by the editorial staff))
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Asymmetric Hydrolysis

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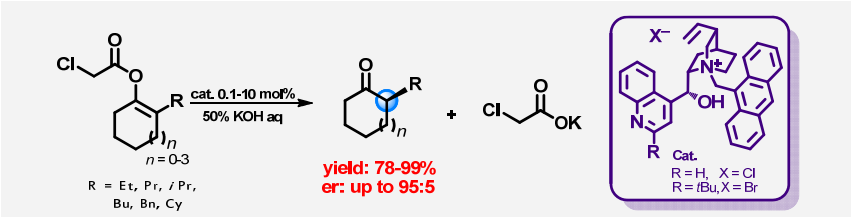

Like an enzyme: Asymmetric hydrolysis of enolesters is accomplished by chiral phase transfer catalysts under bi-phasic base hydrolysis conditions. Stoichiometric reactions support generation of a well-organized chiral ammonium hydroxide species (Q^+OH^-).