Nonenzymatic Kinetic Resolution of Racemic Alcohols through an "Induced Fit" Process

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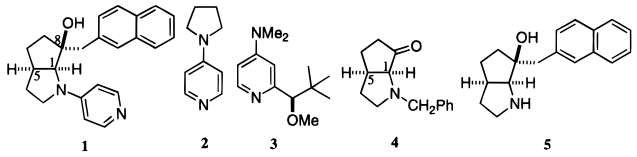
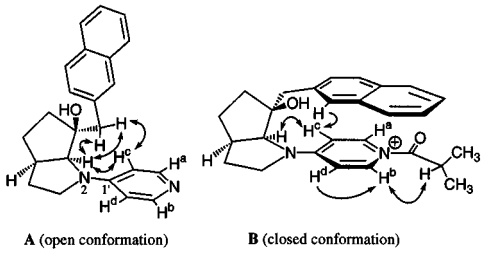
Enzymatic kinetic resolution of racemic alcohols through acylation or deacylation has been extensively studied[1] and established as one of the most effective methods for the preparation of optically active alcohols.[2] Nonenzymatic alternatives in this field have also been developed recently. Use of stoichiometric amounts of chiral acylating agents effected the kinetic resolution with high stereoselectivity.[3] On the other hand, the corresponding catalytic process is still in the developmental stage. The first example was reported by Vedejs *et al*. that chiral phosphines catalytically promoted the kinetic resolution in 9−81% ee (*s* value[4] = 1.2−15).[5] We report here a development of a new nucleophilic catalyst **1**. Catalyst **1** promotes the kinetic resolution of racemic alcohols through enantioselective acylation at ambient temperature. Use of 5 mol % of the catalyst leads to the recovery of optically active alcohols of 92 to >99% ee at 68−77% conversion (*s* = 4.7−12.3). Investigation of the reaction mechanism suggests that **1** acts through an "induced fit" mechanism like natural enzymes, despite its low molecular weight ($C_{23}H_{24}N_2O$ = 344).



1 2 3 4 5

In designing the catalyst, we focused on how strict stereocontrol could be realized without retarding its catalytic activity. We chose 4-pyrrolidinopyridine (PPY) (**2**) as a model of the active site because it is known to be the most effective catalyst for the acylation of alcohols.[6] To achieve effective stereocontrol, a conventional strategy would involve the introduction of sterically demanding asymmetric center(s) near the active site (pyridine nitrogen). However, this would lead to a dramatic reduction in the catalytic activity. For example, the chiral analogue **3**, recently reported by Vedejs,[3c] does not have catalytic activity for the acylation of alcohols, although it does promote the kinetic resolution of secondary alcohols with high stereoselectivity when used in stoichiometric amounts. To overcome the *selectivity*−*reactivity dilemma*, we designed catalyst **1** in which stereocontrolling chiral centers are located far from the active site. This catalyst is expected to cause remote asymmetric induction through chirality transfer from the C(1) and C(8) chiral centers to the active site (*N*-acyliminium) in the reactive intermediate (Figure 1).



A (open conformation) **B** (closed conformation)

Figure 1. ^{1}H NMR study of **1** (**A**) and its acyliminium ion (**B**) in $CDCl_3$ at 20 °C. Arrows denote the observed NOEs. In **A**, protons H^a, H^b, and H^c, H^d appear at δ 8.01 and 6.37 ppm, respectively. In **B**, protons H^a, H^b, H^c, and H^d appear independently at δ 7.45, 8.73, 5.69, and 6.87 ppm, respectively.

Catalyst **1** was prepared from a racemic ketone **4**.[7] Addition of 2-(lithiomethyl)naphthalene (prepared from 2-methylnaphthalene and *n*-BuLi) to **4** followed by hydrogenolysis gave **5** in 80% yield. Racemic **5** was resolved by recrystallization of the salt obtained with (−)-camphorsulfonic acid to give **5** in enantiomerically pure form (>99% ee; absolute configuration: see Supporting Information). A pyridine moiety was introduced into **5** by treatment with 4-chloropyridine and tripropylamine to give **1** in 46% yield, $[\alpha]_D^{17}$ −188° (*c* 1.0, $CHCl_3$). The absolute configuration of levorotatory **1** was determined to be 1*S*,5*R*,8*S* since (1*S*,5*R*)-**4**[7] afforded levorotatory **1** through the same sequence as above. With the use of catalyst **1**, the kinetic resolution of racemic alcohols **6** and **8**−**11** was examined (Table 1).[8] Treatment of racemic **6a** with 5 mol % of **1** and 0.7 molar equiv of isobutyric anhydride[9] in toluene at ambient temperature gave **7a** (R = ^{i}Pr) and recovered **6a** in yields of 60% and 27%, respectively. The optical purity of recovered **6a** was 76% ee (*s* = 4.3, entry 1). With pivaloate **6b**, the enantioselectivity increased to 94% ee (*s* = 8.3, entry 2). When benzoate and substituted benzoates **6c**−**f** were used as substrates, a clear tendency was observed: the stronger the electron-donating ability of the aromatic ring, the higher the enantioselectivity of the reaction (*s* = 2.4−12.3, entries 3−6). The enantiomerically pure (>99% ee) **6f** was recovered from the kinetic resolution of racemic *p*-(dimethylamino)benzoate **6f** with 5 mol % of **1** at 72% conversion (entry 6). Even with 0.5 mol % of catalyst **1** (substrate/catalyst, 200:1), the optical purity of the recovered **6f** was 93% ee (entry 7). The kinetic resolution of several racemic mono[*p*-(dimethylamino)benzoate] of diols was examined with 5 mol % of **1**. In both cyclic diol−monoesters **8**−**10** and the acyclic variant **11**, acylation proceeded enantioselectively to give the recovered alcohols with 92−97% ee at 70−77% conversion (*s* = 4.7−8.3).

Toward grasp of the reaction mechanism, the ^{1}H NMR of **1** and its *N*-acyliminium ion were examined in $CDCl_3$ at 20 °C (Figure 1).[10] The observed NOEs suggest that the preferred conformation for **1** is an "open conformation" (**A**), in which

(1) For reviews: (a) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (b) Klibanov, A. M. *Acc. Chem. Res*. **1990**, *23*, 114. (c) Roberts, S. M. *Chimia* **1993**, *47*, 85.

(2) For reviews on preparation of optically active alcohols, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

(3) (a) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett*. **1993**, *34*, 5563. (b) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1994**, 611. (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc*. **1996**, *118*, 1809.

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(5) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem*. **1996**, *61*, 430.

(6) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl*. **1978**, *17*, 569.

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(8) Typical experimental procedure for the kinetic resolution: To a solution of racemic **6f** (132 mg, 0.50 mmol) and **1** (8.6 mg, 0.025 mmol) in 3 mL of toluene was added 2,4,6-collidine (66 μL, 0.50 mmol) and isobutyric anhydride (58 μL, 0.35 mmol). After 3 h of stirring at ambient temperature, the reaction mixture was treated with 0.1 M HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with sat aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/ethyl acetate, 1:1) to give (1*R*,2*S*)-**6f** (29 mg, 22% yield) and **7** (R = *p*-$Me_2NC_6H_4$) (97 mg, 58% yield). The optical purity of **6f** was determined to be >99% ee by HPLC analysis with Daicel Chiralpak AD (^{i}PrOH/hexane, 10:90).

(9) Use of acetic anhydride instead of isobutyric anhydride usually results in the less effective kinetic resolution. For example, kinetic resolution of **6f** using acetic anhydride under otherwise identical conditions in Table 1 gave (1*R*,2*S*)-**6f** in 35% ee at 38% conversion, which corresponds to *s* = 4.9.

(10) Even in $CHCl_3$, **1** could effectively catalyze the kinetic resolution of **6f** (*s* = 9.9).

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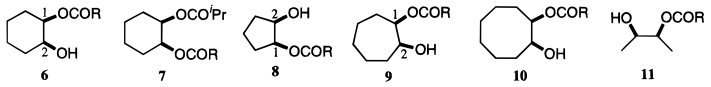
Table 1. Kinetic Resolution of Alcohols **6** and **8**−**11** with Catalyst **1**[a]

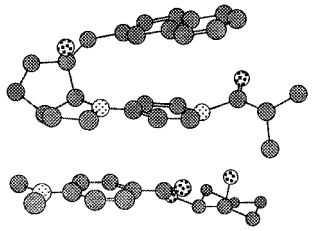


entry	substrate[b]	R	reaction time (h)	conversion (%)	recovery of substrate (%)[c]	optical purity of recovered substrate (% ee)[d]	selectivity[e] (*s*)	absolute configuration[f]
1	**6a**	*i*-Pr	5	69	27	76	4.3	(1*R*,2*S*)
2	**6b**	*t*-Bu	4	68	27	94	8.3	(1*R*,2*S*)
3	**6c**	*p*-$O_2NC_6H_4$	5	73	23	54	2.4	(1*R*,2*S*)
4	**6d**	Ph	5	71	26	81	4.5	(1*R*,2*S*)
5	**6e**	*p*-$MeOC_6H_4$	2	70	27	85	5.3	(1*R*,2*S*)
6	**6f**	*p*-$Me_2NC_6H_4$	3	72	22	>99	>10.1 (12.3)[g]	(1*R*,2*S*)
7[h]	**6f**	*p*-$Me_2NC_6H_4$	5	68	25	93	7.7	(1*R*,2*S*)
8	**8**	*p*-$Me_2NC_6H_4$	4	71	23	97	8.3	(1*S*,2*R*)
9	**9**	*p*-$Me_2NC_6H_4$	4	70	24	92	6.5	(1*R*,2*S*)
10	**10**	*p*-$Me_2NC_6H_4$	5	73	21	92	5.8	*i*
11	**11**	*p*-$Me_2NC_6H_4$	4	77[j]	19	92	4.7	*i*

[a] Substrate (0.5 mmol) was treated with 0.7 molar equiv of isobutyric anhydride and 5 mol % of catalyst **1** in 3 mL of toluene at ambient temperature, unless otherwise stated. [b] Racemic *cis* substrates were used. [c] Isolated yield. Theoretical maximum yield in a kinetic resolution is 50%. [d] Ee was determined by HPLC analysis with chiral columns. See Supporting Information in detail. [e] Ratio of rate constants for the more reactive to the less reactive enantiomer calculated according to ref 4. [f] Absolute configuration was determined by the chemical correlation with configurationally defined monoacetate of the diols. See Supporting Information in detail. [g] At 65% conversion, the recovered substrate (31% yield) showed 97% ee, which corresponds to $s = 12.3$. [h] 0.5 mol % of catalyst **1** was used. [i] Not determined. [j] Isobutyric anhydride (0.8 molar equiv) was used.

the naphthalene ring and the pyridine ring lie apart from each other. Protons H^a and H^b are indistinguishable and appear at δ 8.01 ppm. Similarly, protons H^c and H^d appear at δ 6.37 ppm. These observations indicate free rotation of the N(2)−C(1′) bond and no significant interactions between the naphthalene ring and the pyridine ring. The *N*-acyliminium ion (**B**) is assumed to be the reactive intermediate in the catalytic cycle and was alternatively formed by mixing **1** and isobutyryl chloride in a 1:1 ratio in $CDCl_3$. Protons H^a, H^b, H^c, and H^d appear independently at δ 7.45, 8.73, 5.69, and 6.87 ppm, respectively. The significant upfield shift (0.56−0.68 ppm) of H^a and H^c as well as the downfield shift (0.50−0.72 ppm) of H^b and H^d indicate $\pi-\pi$ interaction between the naphthalene ring and the acylpyridinium moiety. We refer to this conformation as a "closed conformation". Informative NOEs were observed between H^b and the proton, $N^+COCH(CH_3)_2$, which imply that the *si* face of the carbonyl group is blocked by the naphthalene ring and the *re* face is open for reaction with alcohols.

The mechanism of the asymmetric acylation catalyzed by **1** is proposed. Catalyst **1** exists in an "open conformation" (**A**) in its ground state, which is free from steric interaction at the active site. Thus, a facile reaction takes place with acid anhydride. The resulting "closed conformation" of intermediate **B** is suitable for controlling the π-facial reactivity of its *N*-acyliminium moiety, which directs the enantioselectivity of the subsequent acylation of alcohols. The reorganization of the catalyst triggered by binding of the specific substrate (acid anhydride) is referred to as an "induced-fit" process, which is currently recognized as a key process in enzymatic catalysis. As shown in Table 1 entries 3−6, the enantioselectivity of the reaction increases in proportion to the electron-donating ability of the aromatic part of the substrates. This suggests the participation of additional $\pi-\pi$ interaction between the 4-aminopyridinium π-system of **B** and the aromatic ring of the substrates, which is shown as **C** (Figure 2). The $\pi-\pi$ interaction would regulate the direction of the substrate approach. The total catalytic process would result from cooperative and consecutive events at the active site (pyridine nitrogen), the stereocontrolling site (naphthalene moiety), and the binding site (4-aminopyridinium π-system). Although the proposed mechanism is speculative, it is worth noting that catalyst **1** has similar properties as enzymes have acquired only after a long history of evolution.



C

Figure 2. Possible assembly of acyliminium intermediate (**B**) and **6f**.

In summary, we have developed a catalyst **1** for the kinetic resolution of racemic alcohols.[11] A distinctive feature of **1** is its catalyst design based on attractive interaction in nonorganometallic species,[12,13] which is in contrast to the conventional design of catalysts based on repulsive steric interaction in the coordination sphere of the central metal. Catalyst **1** is also expected to catalyze several other types of asymmetric reactions, since PPY (or 4-(dimethylamino)pyridine) has already been shown to catalyze such reactions as peptide bond formation, carbon acylation, and lactonization.[6,14]

Supporting Information Available: Experimental details for preparation of **1** and **5**, characterization data for **1**, **5**, **6a**−**f**, and **8**−**11**, HPLC assay methods for enantiomers of **5**, **6a**−**f**, and **8**−**11**, NOE data for **1** and its acyliminium ion, and the methods for determination of the absolute configuration of **6a**−**f**, **8**, and **9** (38 pages). See any current masthead page for ordering and Internet access instructions.

JA963275G

(11) After completion of this work, papers describing kinetic resolution of racemic alcohols by organometallic catalysts have been published: (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230. (b) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543.

(12) Attractive interaction has been claimed[2a] and recently utilized for the design of chiral catalysts: (a) Corey, E. J.; Loh, T.-P. *J. Am Chem. Soc.* **1991**, *113*, 8966. (b) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794.

(13) For a recent example of nonorganometallic chiral catalysts, see: Iyer, M. S.; Gigstad, K. M.; Namdev. N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.

(14) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.