

Kinetic Resolution of Racemic Alcohols by a New Nucleophilic Catalyst

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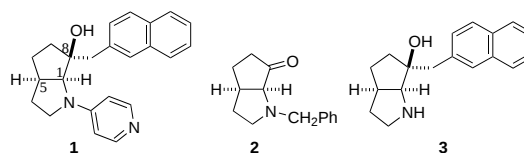
A new nucleophilic catalyst **1** promotes the kinetic resolution of racemic alcohols through enantioselective acylation at ambient temperature. The Key feature of **1** involves an induced fit intermediate due to the π - π interaction, although **1** exists in the open conformation in the ground state.

Keywords : Kinetic resolution/ Acylation/ Nucleophilic catalyst/ Diol

Enzymatic kinetic resolution of racemic alcohols through acylation or de-acylation has been extensively studied and established as one of the most effective methods for the preparation of optically active alcohols. Non-enzymatic alternatives in this field have also been developed recently. Use of stoichiometric amounts of chiral acylating agents effected the kinetic resolution of racemic alcohols with high stereoselectivity.¹ On the other hand, the corresponding catalytic process is still in the developmental stage. We report here development and properties of a new nucleophilic catalyst **1**.²

In designing the catalyst, we focused on how strict stereocontrol could be realized without retarding its catalytic activity. We chose 4-pyrrolidinopyridine as a model of the active site because it is known to be the most effective catalyst for the acylation of alcohols. 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. To overcome the

selectivity-reactivity dilemma, we designed catalyst **1** in which stereo-controlling 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).

Catalyst **1** was prepared from a known racemic ketone **2**. Addition of 2-lithiomethylnaphthalene to **2** followed by hydrogenolysis gave **3** in 80% yield. Racemic **3** was resolved by recrystallization of the salt obtained with (-)-camphorsulfonic acid to give **3** in enantiomerically pure form. A pyridine moiety was introduced into **3** by the palladium-catalyzed coupling with 4-bromopyridine to

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Scope of Research

The research interests of the laboratory include the development of new synthetic methodology, molecular recognition, and screening of antitumor natural products. Programs are active in the areas of use of chiral leaving groups for an asymmetric induction, desymmetrization of symmetrical compounds, asymmetric alkylation of carbonyl compounds based on "memory of chirality", use of binaphthalenes in the asymmetric Wittig-type reactions, syntheses of molecular switch, and Taxus diterpenoids.



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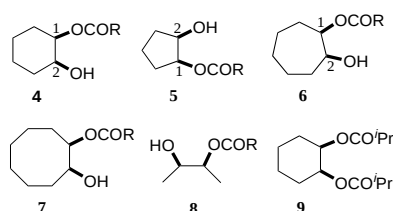
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give **1** in 84% yield. Using catalyst **1**, the kinetic resolution of racemic alcohols **4-8** was examined. Treatment of racemic **4a** (R=*i*Pr) with 5 mol % of **1** and 0.7 mol equivalent of isobutyric anhydride in toluene at ambient temperature gave **9** and recovered **4a** in yields of 60% and 27%, respectively. The optical purity of recovered **4a** was 76% ee. With pivalate **4b** (R=*t*Bu), the enantioselectivity increased to 94% ee. When benzoate and substituted benzoates 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. The enantiomerically pure (>99% ee) alcohol **4c** (R=*p*-Me₂NC₆H₄) was recovered from the kinetic resolution of racemic **4c** with 5 mol % of **1** at 72% conversion. Even with 0.5 mol % of catalyst **1** (substrate : catalyst = 200 : 1), the optical purity of the recovered **4c** was 93% ee. The kinetic resolution of several racemic mono(*p*-



dimethylaminobenzoate) of diols was examined with 5 mol % of **1**. In both cyclic diol-monoesters **5-7** and the acyclic variant **8**, acylation proceeded enantioselectively to give the recovered alcohols with 92 ~ 97% ee at 70 ~ 77% conversion.

To obtain insight into the reaction mechanism, the ¹H NMR spectra of **1** and its *N*-acyliminium ion were measured in CDCl₃ at 20 °C (Figure 1). The observed NOE's suggest that the preferred conformation for **1** is an "open conformation" (A), in which 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

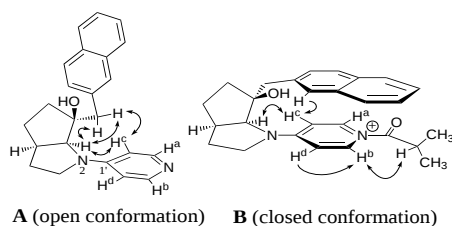


Figure 1. ¹H NMR study of **1** (A) and its acyliminium ion (B) in CDCl₃ at 20 °C. Arrows denote the observed NOE's. In A, protons H^a, H^b and H^c, H^d appear at δ 8.01 and 6.37 ppm, respectively. In B, protons H^a, H^b, H^c, and H^d appear independently at δ 7.45, 8.73, 5.69, and 6.87 ppm, respectively.

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 CDCl₃. 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 π-π interaction between the naphthalene ring and the acyliminium moiety. We refer to this conformation as a "closed conformation". Informative NOE's were observed between H^b and the proton, N⁺COCH(CH₃)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.

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 acyliminium intermediate (B) is stabilized by attractive π-π interaction between the electron-deficient acyliminium π-system and the electron-donating naphthalene ring. The "closed conformation" is suitable for controlling the π-facial reactivity of the *N*-acyliminium ion, 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. Since the enantioselectivity of the reaction increases in proportion to the electron-donating ability of the aromatic part of the substrates, it is suggested that the participation of additional π-π interaction between the 4-aminopyridinium π-system of B and the aromatic ring of the substrates. The π-π interaction involving the substrate-binding and -recognizing properties of catalyst **1** 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 stereo-controlling 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.

In summary, we have developed a catalyst **1** for the kinetic resolution of racemic alcohols. The properties of **1** appear to approach some of the enzymatic functions with regard to mildness of the reaction conditions, enantioselectivity, and the reaction mechanism. Another distinctive feature of **1** is its catalyst design based on attractive interaction in non-organometallic species, 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 in addition to the kinetic resolution of alcohols such as peptide-bond formation, carbon-acylation, and lactonization.

References

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