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Kinetic resolution of *sec*-alcohols by a new class of pyridine catalysts having a conformation switch system

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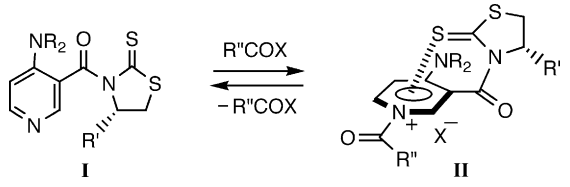
Abstract—The catalysts having a conformation switch system induced by acylation and deacylation serve as asymmetric acylating catalysts of *sec*-alcohols. The kinetic resolution of various *sec*-alcohols resulted in good to excellent selectivities in the presence of 0.5 to 0.05 mol % of catalyst **1a**. The conformation switch system plays a key role to attain both good selectivity and high catalytic activity.

Kinetic resolution is an effective method for obtaining chiral *sec*-alcohols. Various types of non-enzymatic acyl-transfer organocatalysts[1] such as chiral phosphines,[2,3] diamines,[4] 4-aminopyridine analogues,[5] peptide-based catalysts,[6,7] dihydroimidazopyridines,[8] and N-heterocyclic carbenes[9] have extensively been explored, and the catalytic acylations are achieved by them in high enantioselectivities. Nevertheless, further development of a new class of acylating catalysts has continued to be an important challenge in synthetic organic chemistry.

We have recently found a new type of cation–π interaction[10] between a pyridinium ring and a thiocarbonyl group.[11] This interaction was utilized for the selective shielding of the pyridinium face by the thiocarbonyl group, which enabled nucleophiles to attack the opposite side to give chiral 1,4-dihydropyridines.[12] This result suggests a new conformation switch system based on the interconversion between uncomplexed form I and self-complexed form II induced by N-acylation and deacylation steps as shown in Scheme 1. We planned to develop new asymmetric acylating catalysts having this conformation switch system because this system would play a key role to attain both high catalytic activity and selectivity in the kinetic resolution; the formation of cation–π complex II enables discrimination of enantiomeric *sec*-alcohols and the uncomplexed form I causes smooth N-acylation for the next catalytic cycle. This concept seems to be related to an induced-fit process proposed by Kawabata et al.[13]



Scheme 1.

Recently, several groups have extensively developed pyridine catalysts for asymmetric acylation of alcohols. The key feature of the catalytic reactions is selective blocking of the pyridinium ring by an aromatic moiety such as pentaphenylcyclopentadienyl,[14] naphthyl,[13] binaphthyl,[15] biaryl,[16] and substituted aryl[17]group; however, a non-aromatic system has not yet been reported. In this letter, we report a new class of pyridine catalysts having a conformation switch system, which serve as practical asymmetric acylating catalysts for *sec*-alcohols.

We prepared 4-dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) analogues **1**–**4** possessing chiral thiazolidine-2-thione, oxazolidine-2-thione or oxazolidine-2-one. These catalysts can be readily prepared from 4-aminonicotinic acid obtained from commercially available 4-chloropyridine with the chiral auxiliary.[18] Acylation of 1-(2-naphthyl)ethanol (**8**) with

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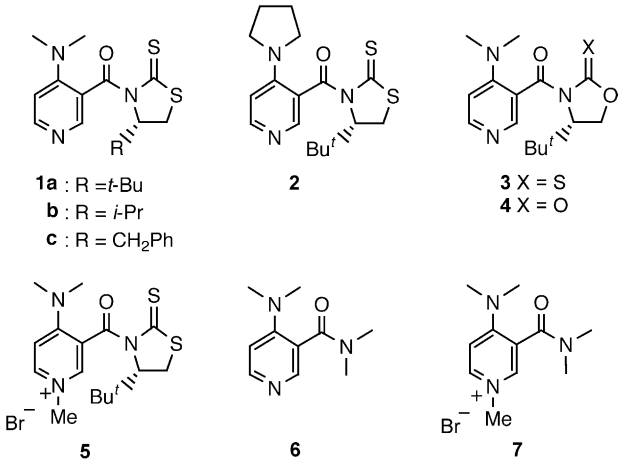
isobutyric anhydride smoothly proceeded in the presence of 5 mol % of catalysts **1**–**4** in toluene at 0 °C (Table 1, entries 1–6). The selectivity[19] largely depends on the substituent of the catalysts; compound **1a** having a bulky *tert*-butyl group provides the highest selectivity among **1a**–**c**. Compounds **2** and **3** also served as effective acylating catalysts, whereas **4** was less effective, suggesting the importance of the C=S group to attain high enantioselectivity. The absolute configuration of the recovered alcohol was assigned to be *S* by comparison of the specific rotation with that of the literature.

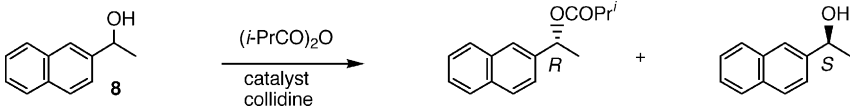


A survey of acylating reagents revealed that isobutyric anhydride afforded the highest selectivity among the anhydrides that we have investigated. The solvents significantly affect the *s* values (entries 7–11); use of acyclic ethers Et_2O, *i*-Pr_2O, and *t*-BuOMe remarkably improved the selectivities (entries 9–11), whereas polar solvents were less effective (entries 7 and 8). The reaction temperature is also an important factor to attain high stereoselectivity (entries 11–13); lowering the temperature increases the *s* value. We next studied the effect of the catalyst amount on the reactions (entries 12, 14, and 15). Reducing the catalyst amount from 5 mol % to 0.5 mol % had little effect on the *s* value, and the reactions were completed within 12 h. Remarkable is that the further reducing of the catalyst to 0.05 mol % resulted in the same selectivity as in the case of entry 14, though the reaction required 72 h to reach 55% conversion.

This method is applicable to various *sec*-alcohols as shown in Table 2. Acylation of 1-phenylethanol (**9**) with isobutyric anhydride in the presence of 0.5 mol % of **1a** and Et_3N[21] gave good selectivity. The electron-donating and withdrawing groups at the *p*-position on **10** and **11**, respectively, had little effect on the *s* values. This indicates that the intermolecular interaction described later is so stronger that the selectivities do not receive the substituent effect. These conditions are also effective for sterically hindered alcohol **12**. Kinetic resolution of 1-(1-naphthyl)ethanol (**13**) gave a similar result to that of its isomer **8**. This method is applicable for heterocyclic *sec*-alcohol **14**, and allylic and propargylic alcohols **15** and **16**; lowering the temperature to −30 °C much improved the selectivities. In most cases the *s* values are larger than 7, showing the practical usefulness of this method.[19]

^{1}H NMR studies of **1a**, **5**–**7** and *N*-isobutyryl form of **1a** provided insight into the reaction mechanism. Figure 1 shows $\Delta\delta$**1a** and $\Delta\delta$**5**,[22] which are differences between δ**1a** and δ**6** and δ**5** and δ**7**, respectively. These values reflect the effect of the thiocarbonyl moiety on the pyridine and the pyridinium protons. Comparison of the $\Delta\delta$**1a** and the $\Delta\delta$**5** clarified significant differences between them. The $\Delta\delta_{H2}$ and $\Delta\delta_{H6}$ values for **5** are

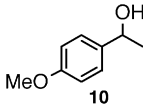
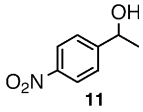
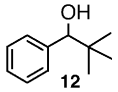
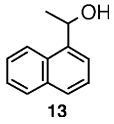
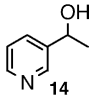
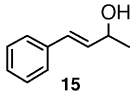
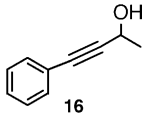
Table 1. Kinetic resolution of 1-naphthylethyl alcohol catalyzed by **1**–**4**[a]



Entry	Cat (mol%)	Solvent	Temp (°C)	Time (h)	Conv[b] (%)	ee (%)	*s*[c]
1	**1a** (5)	Toluene	0	3	59	87	11
2	**1b** (5)	Toluene	0	3	55	74	9.1
3	**1c** (5)	Toluene	0	3	58	73	7.0
4	**2** (5)	Toluene	0	3	61	88	9.8
5	**3** (5)	Toluene	0	3	57	82	11
6	**4** (5)	Toluene	0	3	53	37	2.7
7	**1a** (5)	CH_3CN	0	3	61	68	5.0
8	**1a** (5)	THF	0	3	60	80	7.6
9	**1a** (5)	Et_2O	0	3	61	96	15
10	**1a** (5)	*i*-Pr_2O	0	3	50	78	19
11	**1a** (5)	*t*-BuOMe	0	3	57	95	24
12	**1a** (5)	*t*-BuOMe	25	3	64	99	18
13	**1a** (5)	*t*-BuOMe	−30	5	56	97	30
14	**1a** (0.5)	*t*-BuOMe	25	12	57	92	17
15	**1a** (0.05)	*t*-BuOMe	25	72	55	87	17

[a] 0.7 equiv of (*i*-PrCO)$_2$O and 0.8 equiv of collidine were used.
[b] Conversion (%) = ee of recovered **8**/(ee of recovered **8** + ee of ester), see Ref. 20.
[c] Selectivity factor *s* = *k*(fast-reacting enantiomer)/*k*(slow-reacting enantiomer), see Ref. 19.

Table 2. Kinetic resolution of various alcohols catalyzed by **1a**[a]

Substrate	% ee[b] (config)[c]	s[d] (% conv)[e]
 **9**	89 (*S*)	7.6 (65)
 **10**	97 (*S*)	10 (68)
 **11**	98 (*S*)	8.9 (72)
 **12**	88[f] (*S*)	9.6 (62)
 **13**	97 (*S*)	13 (65)
 **14**	92 (*S*)	8.1[e] (66)
 **15**	94 (*S*)	9.8[e] (65)
 **16**	78 (*S*)	6.6[e] (61)

[a] All reactions were conducted in the presence of 0.5 mol % of **1a**, 0.8 equiv of $(Pr^iCO)_2O$ and 0.9 equiv of Et_3N at rt for 12 h unless otherwise noted.
[b] Determined by HPLC using chiral stationary phases.
[c] Conversion (%) = ee of recovered alcohol/(ee of recovered alcohol + ee of ester), see Ref. 20.
[d] Selectivity factor $s = k$(fast-reacting enantiomer)/k(slow-reacting enantiomer), see Ref. 19.
[e] −30 °C, 48 h.
[f] The reaction time is 72 h.

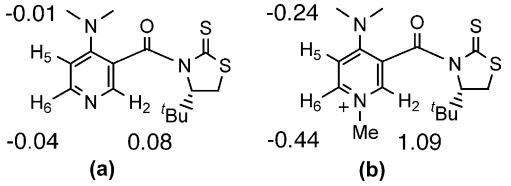


Figure 1. (a) Δδ**1a** values and (b) Δδ**5** values.

1.09 and −0.44, respectively, the absolute values of which are much larger than those of **1a** (0.08 and 0.04). These observations are comparable with those of a previously reported cation–π complex having a thiocarbonyl group and a pyridinium ring,[11] strongly suggesting the existence of an intramolecular interaction in pyridinium salt **5**.

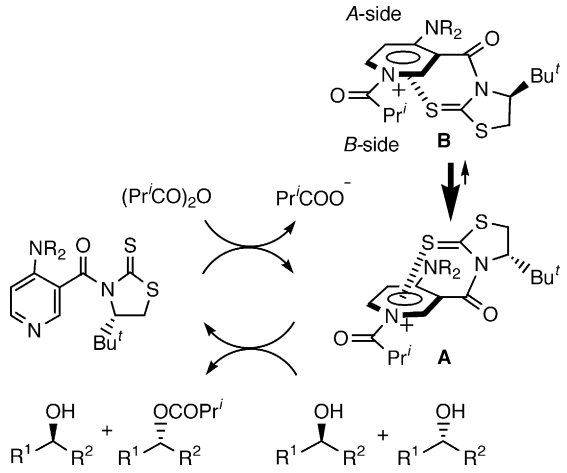


Figure 2. Plausible catalytic cycle.

Figure 2 shows a plausible catalytic cycle. Acylation of the catalyst with isobutyric anhydride gives conformationally locked *N*-acylpyridinium salt **A** as a result of an intramolecular cation–π interaction. This conformation is clarified by NOE experiments[23] and DFT calculations.[24] One of two enantiomers of racemic *sec*-alcohols preferentially attacks the intermediate **A** from *B*-side[25] to give the corresponding ester with recovery of the catalyst. The catalyst restored conformational freedom undergoes smooth N-acylation of the next cycle.

The stereoselectivity can be explained by comparison of the two transition state models TS-I and TS-II for the acylation of (*R*)- and (*S*)-alcohols, respectively, as shown in Figure 3. Both alcohols would approach the pyridinium ring from *B*-side with face to face orientation due to a cation–π interaction between the pyridinium ring and the phenyl ring.[26] While (*R*)-alcohol can effectively approach the *N*-acyl group, (*S*)-alcohol receives significant steric repulsion with the amide moiety during approaching the *N*-acyl group; therefore, the acylation preferentially proceeds through TS-I to give (*R*)-ester predominantly.

In summary, we have developed a new class of acylating catalysts having a conformation switch system. The catalytic kinetic resolution of various *sec*-alcohols resulted in good to excellent selectivities in the presence of 0.5–0.05 mol % of catalyst. These catalysts have compact structures with small molecular weights. In addition, they are easily prepared from a commercially available

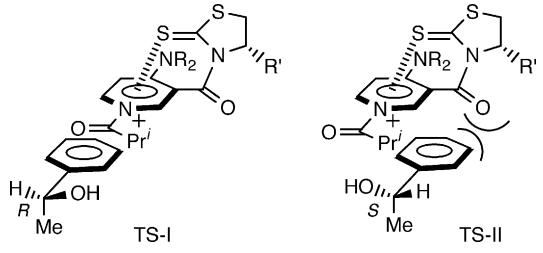


Figure 3. Schematic favored (TS-I) and disfavored (TS-II) transition structures for acylation of *S* and *R* alcohols, respectively.

pyridine compound with a chiral auxiliary. These features clearly show a significant synthetic utility of these catalysts from a practical point of view.

Acknowledgements

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21. Triethylamine was used instead of collidine because of little difference in the selectivities.
22. The *N*-isobutyryl form of **1a** is in equilibrium with **1a**, in addition, the chemical shifts of the pyridinium protons receive an anisotropic effect from the *N*-acyl carbonyl group. Therefore, *N*-methylpyridinium salt **5** was used instead of *N*-isobutyryl form of **1a** to neglect such inadequate effects for evaluation of the intramolecular interaction.
23. NOE experiments of *N*-isobutyryl form of **1a** clarified that the *N*-acyl carbonyl oxygen is close to H6. Irradiation of H2 and H6 resulted in 17.6% and 0.5% NOEs for COCH proton, respectively.
24. DFT calculations at the B3LYP/6-31G* level suggested that conformer **A** where the C=S group blocks the A-side of the pyridinium is 1.02 kcal/mol more stable than conformer **B**.
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