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Dynamic kinetic resolution of hemiaminals using a novel DMAP catalyst

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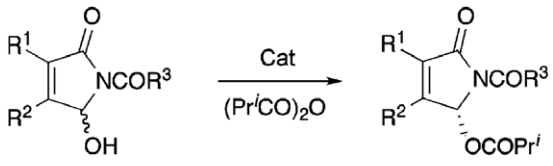
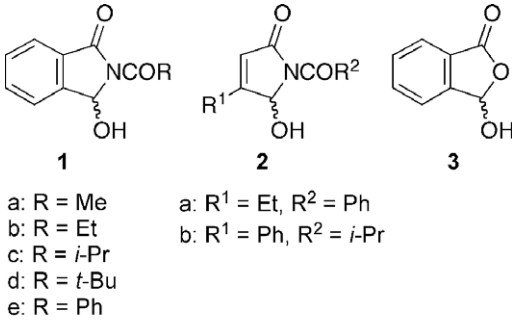
Abstract—We describe the first catalytic dynamic kinetic resolution of hemiaminals mediated by an organocatalyst. A 0.1–1 mol % catalyst loading is effective for the dynamic kinetic resolution of hemiaminals to produce esters up to 88% ee in high yields. A 10 mol % catalyst loading resulted in a decreased selectivity, whereas the selectivity increased at 50 °C. The absolute configuration is assigned on the basis of the empirical Cotton effect rule.

Enzymatic dynamic kinetic resolution (DKR) of *sec*-alcohols by way of asymmetric acylation has attracted significant interest because it provides optically active esters in up to 100% yield,[1] and therefore, this procedure has been applied to a variety of organic syntheses. As substrates for this procedure, hemiacetals and hemiaminals are promising candidates due to their capability of in situ racemization through tautomerism.[2,3] In addition, the product esters have been used as chiral building blocks for various organic syntheses.[4]

We previously reported the nonenzymatic DKR of hemiaminals by acylation with chiral acylating reagents.[5] Moreover, we recently developed a novel dimethylaminopyridine (DMAP) catalyst, which was effective for the kinetic resolution of racemic *sec*-alcohols[6,7] and desymmetrization of *meso*-diols.[7] These findings prompted us to investigate the catalytic kinetic resolution of hemiaminals (Scheme 1). In this Letter, we describe that our catalyst is also effective for the DKR of hemiaminals. To the best of our knowledge, this is the first example of the organocatalyst mediated DKR of hemiaminals.



Scheme 1. DKR of hemiaminals through asymmetric acylation.



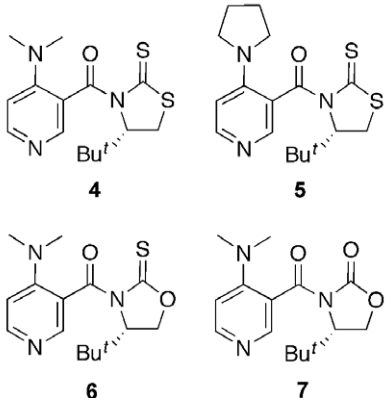


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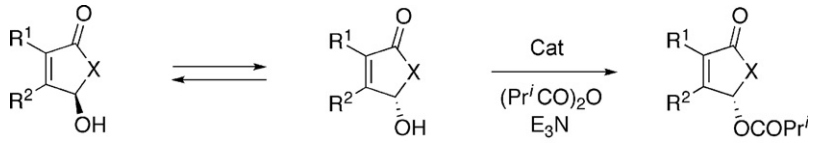
Table 1. Catalytic dynamic kinetic resolution of **1**–**3**



1-3 **8-10**

Entry	Substrate	Cat[a]	Solv.	Product	Time (h)	Yield[b] (%)	ee[c] (Config.)[d] (%)
1	**1a**	**4**	*t*-BuOMe	**8a**	23	98	82
2	**1b**	**4**	*t*-BuOMe	**8b**	11	>99	84 (*R*)
3	**1c**	**4**	*t*-BuOMe	**8c**	8	>99	88 (*R*)
4	**1d**	**4**	*t*-BuOMe	**8d**	8	98	87
5	**1e**	**4**	*t*-BuOMe	**8e**	23	95	66 (*R*)
6	**1c**	**5**	*t*-BuOMe	**8c**	8	>99	82 (*R*)
7	**1c**	**6**	*t*-BuOMe	**8c**	8	99	87 (*R*)
8	**1c**	**7**	*t*-BuOMe	**8c**	8	98	70 (*R*)
9	**1b**	**4**	Toluene	**8b**	11	99	79 (*R*)
10	**1b**	**4**	CH_2CI_2	**8b**	11	>99	65 (*R*)
11	**1b**	**4**	THF	**8b**	11	99	82 (*R*)
12	**1b**	**4**	*c*-PentylOMe	**8b**	11	99	84 (*R*)
13	**2a**	**4**	*t*-BuOMe	**9a**	8	94	49 (*R*)
14	**2b**	**4**	*t*-BuOMe	**9b**	24	86	24 (*R*)
15	**3**	**4**	*t*-BuOMe	**10**	8	>99	40 (*R*)

[a] 1 mol % of catalyst was used.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.
[d] Absolute configuration was assigned based on the Cotton effect of the CD spectra.

The dynamic kinetic resolution of hemiaminals **1** and **2** and hemiacetal **3** by catalytic acylation with 1 mol % of catalysts **4**–**7** was investigated under various reaction conditions as shown in Table 1. The acylation of hemiaminals **1a**–**e** with isobutyric anhydride and triethylamine in the presence of catalysts **4** gave the corresponding esters in high yields with 66–88% ee, clearly suggesting that the DKR effectively occurred in this system (entries 1–5).[8] The selectivity depends on the substituent at the *N*-acyl group of the hemiaminals; the acylation of **1c** and **1d** having isobutyroyl and pivaloyl groups, respectively, resulted in the high selectivities (entries 3 and 4). This indicates that the steric bulkiness around the *N*-acyl group would be important for the discrimination of racemic alcohols. Among the DMAP derivatives **4**–**7**, **4**–**6** serve as effective catalysts (entries 3 and 6–8). Since a similar trend is observed in the kinetic resolution of *sec*-alcohols, the importance of the C=S group for the stereoselectivity would be a common feature in the catalytic acylations with this series of catalysts.[7] A survey of solvents revealed bulky ethers to be effective (entries 2 and 9–11).

The catalytic acylation of monocyclic hemiaminals **2a** and **2b**[9] gave the corresponding esters in good yields with 49% and 24% ee, respectively (entries 13 and 14). The relatively lower stereoselectivities in comparison with the case of hemiaminals **1** indicated that the condensed aromatic ring would have a significant effect on the enantioselectivity. It is worthwhile noting that the catalytic DKR of hemiacetal **3** resulted in a 40% ee with the opposite stereoselectivity compared to the case of **1**, suggesting the importance of the *N*-acyl moiety on the selectivity (entry 15).

The absolute configurations of the product esters were determined by a CD spectral analysis according to the empirical rule proposed by Feringa and co-workers[10] in which the signs of the Cotton effects of the n–π* and π–π* transitions are correlated to the absolute configuration. The CD spectrum of **8c** shows positive n–π* (245 nm) and negative π–π* (208 nm) Cotton effects, which allowed assigning the *R* configuration to the stereogenic center (Fig. 1). The absolute configurations of esters **8** were all assigned in a similar manner. On the other hand, the opposite sign pattern observed for **9** allowed assigning the *R* configuration.

Next, the effect of the catalyst amount on the selectivity was investigated for **1b** and **2b** using catalyst **4** (Table 2). The DKR of **1b** with 0.1 mol % of catalyst **4** quantitatively gave **8b** in 75% ee (entry 1). The reaction at 0 °C required 139 h for completion of the reaction, but the stereoselectivity was improved to 83% ee (entry 2). A 1 mol % loading of the catalyst significantly accelerates the reaction and slightly increased the selectivity compared to the 0.1% loading (entry 3). Interesting is the fact that the increasing amount of the catalyst from 1

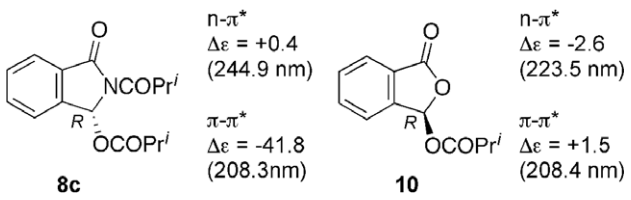
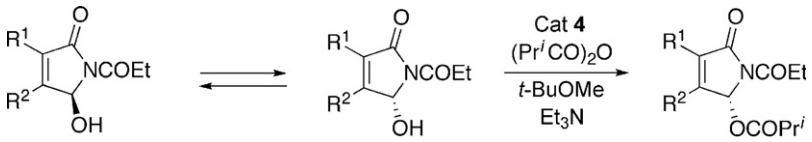


Figure 1. Determination of the absolute configurations of the products by CD Cotton effects.

Table 2. Effects of catalyst amount and temperature on the selectivity



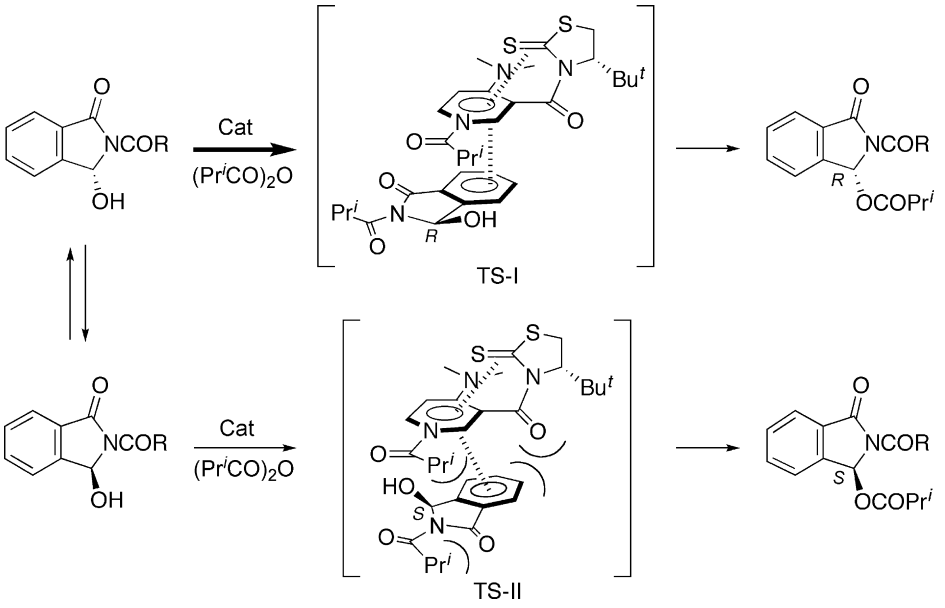
1b or **2b** **8b** or **9b**

Entry	Aminal	Cat (mol %)	Temperature	Time (h)	Yield[a] (%)	ee[b] (Config.)[c] (%)
1	**1b**	0.1	rt	72	>99	75 (*R*)
2	**1b**	0.1	0	139	>99	83 (*R*)
3	**1b**	1	rt	9	96	79 (*R*)
4	**1b**	10	rt	2	96	63 (*R*)
5	**1b**	10	50	0.5	>99	74 (*R*)
6	**2b**	1	rt	24	86	24 (*R*)
7	**2b**	1	50	24	90	45 (*R*)

[a] Isolated yield.
[b] Determined by HPLC with chiral columns.
[c] Absolute configuration was assigned based on the Cotton effect of the CD spectra.

to 10 mol % caused a significant decrease in the selectivity (entry 4). However, surprisingly, the selectivity was much improved to 74% ee by raising the temperature to 50 °C. A similar phenomenon was observed in the DKR of **2b**; the selectivity at 50 °C is higher than that at rt (entries 6 and 7). These unusual observations where the selectivity decreased with the increasing amount of the catalyst while the selectivity increased by raising the reaction temperature are attributable to the changes in the relative rates between the acylation and racemization steps. Thus, a 10 mol % catalyst loading caused much faster acylation than the racemization of the substrate, and as a result, the selectivity decreased. On the contrary, raising the temperature to 50 °C would more effectively enhance the racemization than the acylation, which resulted in the increased ee.

Although exact mechanism for this DKR is still unclear, the *R*-selectivity in this reaction can be explained by the following transition state models regarding the stable conformations of the catalyst and the substrate (Scheme 2). In our previous studies,[7] the catalyst is predicted to have a self-complexed conformation as shown in Scheme 2. On the other hand, the X-ray crystallographic analysis[11,12] and DFT calculations[13] for **1c** suggested the existence of a hydrogen bond between the oxygen atom of the hydroxy group and the *N*-acylcarbonyl group with the distance of 2.988 and 2.743 Å, respectively (Fig. 2). Each enantiomeric hemiaminal would approach the unblocked side of the pyridinium face with a face-to-face orientation between the pyridinium and the aromatic rings through an intermolecular cation–π interaction. As shown in TS-I and TS-II, the (*R*)-alcohol preferentially attacks the *N*-acyl group rather than the (*S*)-alcohol because the (*S*)-alcohol receives a considerable steric repulsion by the carbonyl and the isopropyl group, and as a result, the (*R*)-ester was predominantly produced via TS-I. This can explain the higher selectiv-



Scheme 2. Plausible mechanism for DKR of **1**.

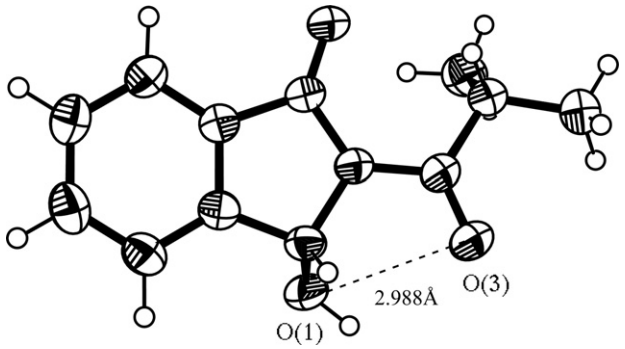


Figure 2. ORTEP drawing for **1c** at the 50% probability level.

ity for hemiaminals **1b–d** having both a condensed aromatic ring and a bulky *N*-acyl group.

In summary, we described the first catalytic dynamic kinetic resolution of hemiaminals mediated by an organocatalyst. A 0.1–1 mol % catalyst loading is effective for the DKR of hemiaminals to give esters up to 88% ee in high yields. Controlling the relative rates between the racemization and the acylation steps was essential to the success of this DKR. The proposed transition state model can explain the resulting stereochemical outcome, in which the cation–π interaction might play a key role.

Acknowledgment

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References and notes

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8. *A typical procedure for the dynamic kinetic resolution of hemiaminals*: To a solution of hemiaminal **1c** (30 mg) and 1 mol % of catalyst **4** (447 μL of 3.1 mmol L^{-1} solution) in 1 mL of *t*-BuOMe were added Et_3N (21 μL) and isobutyric anhydride (25 μL) at 0 °C. The solution was stirred for 8 h at rt. MeOH was added to the reaction mixture, and the solution was stirred for 20 min. The reaction mixture was concentrated and the residue was purified by preparative TLC (hexane/AcOEt = 4/1) to give the product ester **8c** (40.0 mg). The enantiomeric excess of the ester was determined by HPLC analysis using Daicel CHIRALPAK AD column using 9:1 mixture of hexane and *i*-PrOH as an eluent solvent.
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11. *X-ray crystal data for* **1c**: $C_{12}H_{13}NO_3$, $M = 219.24$, monoclinic, $P2_1/c$, $a = 11.1726(6)$, $b = 7.1147(4)$ $c = 13.6512(6)$ Å, $\beta = 98.083(3)°$, $V = 1074.36(9)$ A^3, $T = 298$ K, $Z = 4$, $Dc = 1.256$ g cm^{-1}. A total of 11711 reflections were collected and 1944 are unique ($R_{int} = 0.052$). R_1 and wR_2 are 0.0365 [$I > 2\sigma(I)$] and 0.1050 (all data), respectively. CCDC 661154.
12. The distance between the hydrogen atom of HO(1) and O(3) atom is ca. 2.6 Å and that for O(1) and O(3) is 2.998 Å which is within a range of general O–H···O hydrogen bond.
13. The DFT calculations were performed at the B3LYP/6-31G* level by using Spartan 06'. The calculations predicted only one stable conformer in which two carbonyl groups have an opposite direction with a hydrogen bonding between the hydroxy group and the carbonyl group.