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Kinetic Resolution of 2-Oxazolidinones via Catalytic, Enantioselective N-Acylation

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Kinetic resolution (KR)[1] of racemic alcohols[2] and amines[3] via enzyme-catalyzed enantioselective acyl transfer is well-known. Many nonenzymatic catalysts, which have been developed over the past decade, allow catalytic, enantioselective O-acylation of alcohols.[4] In contrast, there is to date only one report describing the analogous N-acylation of amines.[5] To the best of our knowledge, catalytic, enantioselective N-acylation of another common class of nitrogen nucleophiles—chiral secondary amides—has not been achieved previously using either enzymes or synthetic catalysts. Unlike amines, which can often be resolved via crystallization of their diastereomeric salts with chiral acids, amides are not basic enough to form stable salts. The development of enantioselective acylation of racemic amides would thus provide a convenient means of achieving their resolution.[6] In this communication, we report the first successful examples of this process.

We were encouraged by reports on *achiral* DMAP-catalyzed N-acylation of 4-substituted oxazolidinones with carboxylic acid anhydrides.[7] In addition, various amides, both cyclic and acyclic, are known to be acylated with Boc_2O in the presence of DMAP.[8] Thus, we decided to employ our recently developed DHIP-based enantioselective acylation catalyst **1**[9a,c] to test the feasibility of the asymmetric version of this reaction (Figure 1). Since our earlier experimental observations in KR of benzylic alcohols indicated the importance of $\pi-\pi$ and cation$-\pi$ interactions in the chiral recognition of benzylic alcohols, we chose 4-phenyl-2-oxazolidinone **4a** as the starting point of our study (Figure 2).

In the first, proof-of-principle experiment, substrate **4a** was acylated with propionic anhydride in the presence of CF_3-PIP (**1**), under conditions analogous to those previously employed for benzylic alcohol substrates. After 24 h, the conversion reached 39%, and the selectivity factor[10] was determined to be 7.8. As anticipated on the basis of our model, the *S*-enantiomer of the substrate (configurationally analogous to *R*-alcohols) was acylated preferentially (Scheme 1).

The second-generation catalyst, Cl-PIQ (**2**), developed at that time in our laboratory,[9b] proved to be more effective than **1** and thus was selected for further optimization studies. Lower concentrations were chosen to provide a standard set of conditions for all oxazolidinone substrates **4**−**6**, many of which have only limited solubilities. The selectivity was improved when isobutyric anhydride was substituted for propionic, whereas other anhydrides tested were far less successful (Table 1, entries 1−5). *tert*-Amyl alcohol[11] performed better than chloroform as a reaction media, and both were considerably superior to other solvents screened (cf. entries 3 and 6−10).

The influence of the substrate structure was investigated next. As expected, replacement of the phenyl group with 1- or 2-naphthyl led to increased selectivities (entries 11, 12). Comparable results were obtained with the 2-furyl analogue **4d** (entry 13), while the thiophene derivative **4e** was resolved with lower selectivity than

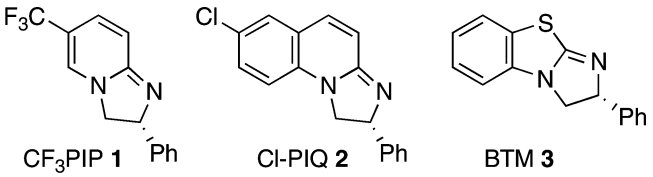
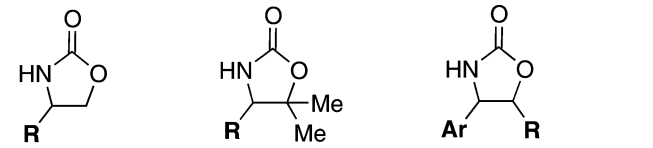


Figure 1. Ring-fused imidazoline catalysts.



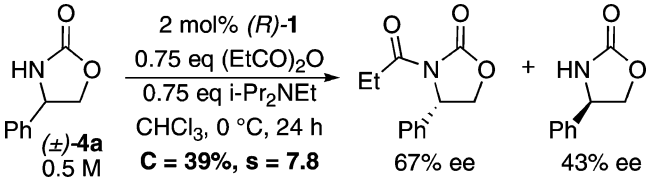
4a: R = phenyl
4b: R = 1-naphthyl
4c: R = 2-naphthyl
4d: R = 2-furyl
4e: R = 2-thienyl
4f: R = isopropyl

5a: R = phenyl
5b: R = 1-naphthyl
5c: R = 2-naphthyl
5d: R = 2-furyl
5e: R = 2-thienyl

6a: Ar = R = Ph (*cis-*)
6b: Ar = R = Ph (*trans-*)
6c: Ar = *p*-$MeOC_6H_4$, R = CO_2Me (*cis-*)
6d: *4R,5R-(-)*-Cytoxazone: Ar = *p*-$MeOC_6H_4$ (β–), R = CH_2OH (β–)

Figure 2. Oxazolidinone substrates.

Scheme 1



4a (entry 14). The importance of π-interactions was confirmed by the absence of any appreciable reaction with the isopropyl-substituted oxazolidinone **4f** even at room temperature (entry 15). *gem*-Dimethyl substituted substrates **5a**−**c** reacted with much higher selectivities than their unsubstituted counterparts **4a**−**c** (entries 16−18 vs 6, 11, 12), whereas in the case of the heteroaryl substrates the differences in selectivity were not significant (entries 19, 20 vs 13, 14). In the case of **5a**, increased catalyst loading was needed to achieve respectable reaction rates. Both *cis*- and *trans*-4,5-diphenyl-2-oxazolidinones (**6a** and **b**, entries 21, 22) were resolved with selectivities and rates comparable to those of substrate **4a**. It should be noted that the limited solubility of some of the oxazolidinones (**4c**, **5b**, **c** and **6a**) in *tert*-amyl alcohol prevented reliable selectivity measurements.[12] Substrate **6c** was practically insoluble in this solvent, which rendered its resolution inefficient ($s < 2$).

In a parallel development in our laboratory, catalyst **3** was synthesized and shown to possess markedly higher enantioselectivity than **2** in the KR of benzylic alcohols.[9d] Naturally, these findings prompted us to test the new catalyst in the KR of 2-oxazolidinones. The results far surpassed our expectations. Acylation of substrates **4a**−**e** and **6a, b** catalyzed by BTM (Table 2, entries 1−7) *proceeded*

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Table 1. KR of 2-Oxazolidinones Using Cl-PIQ (**2**)[a]

entry	substrate	R′	solvent	time (h)	% conv	*s*
1	**4a**	Me	$CHCl_3$	3	43	1.3
2	**4a**	Et	$CHCl_3$	3.5	45	10
3	**4a**	*i*-Pr	$CHCl_3$	24	42	17
4	**4a**	Ph	$CHCl_3$	24	16	−5.5
5[b]	**4a**	t-BuO	$CHCl_3$	24	<3	ND
6	**4a**	*i*-Pr	$EtMe_2COH$	19	44	24
7	**4a**	*i*-Pr	THF	24	17	12
8	**4a**	*i*-Pr	MeCN	24	25	3
9	**4a**	*i*-Pr	EtOAc	24	12	8
10[b,c]	**4a**	*i*-Pr	PhMe	24	7	9
11	**4b**	*i*-Pr	$EtMe_2COH$	17	46	38
12[c]	**4c**	*i*-Pr	$EtMe_2COH$	19	44	44
13	**4d**	*i*-Pr	$EtMe_2COH$	17	50	25
14	**4e**	*i*-Pr	$EtMe_2COH$	15	47	16
15[b]	**4f**	*i*-Pr	$CDCl_3$	16	0	ND
16[d]	**5a**	*i*-Pr	$EtMe_2COH$	21.5	43	55
17[c]	**5b**	*i*-Pr	$EtMe_2COH$	10	40	1.1×10^2
18[e]	**5c**	*i*-Pr	$EtMe_2COH$	10	49	70
19	**5d**	*i*-Pr	$EtMe_2COH$	28	50	28
20	**5e**	*i*-Pr	$EtMe_2COH$	19	49	18
21[c]	**6a**	*i*-Pr	$EtMe_2COH$	24	43	26
22	**6b**	*i*-Pr	$EtMe_2COH$	15	48	19

[a] Unless specified otherwise, the following conditions were used: 0.2 M substrate, 0.75 equiv $(R'CO)_2O$, 0.75 equiv *i*-Pr_2NEt, 4 mol % *(R)*-**2**, 0 °C. [b] RT. [c] Incompletely dissolved substrate at 0.2 M. [d] 8 mol % *(R)*-**2** was used. [e] Incompletely dissolved substrate at 0.1 M.

Table 2. KR of 2-oxazolidinones Using BTM (**3**)

entry	substrate	ee_{SM}[a]	ee_P[a]	time (h)	%conv[a]	*s*[a]
1[b]	**4a**	54.1	98.3	8.5	36	2.0×10^2
2[b]	**4b**	71.6	99.1	21	42	4.5×10^2
3[b]	**4c**	87.6	97.8	14	47	2.6×10^2
4[b]	**4d**	70.5	95.7	8.5	42	96
5[b]	**4e**	96.0	98.2	6	49	4.3×10^2
6[b]	**6a**	71.7	98.5	6	43	3.0×10^2
7[b]	**6b**	72.3	91.8	6	44	50
8[b]	**6c**	96.2	93.2	5.75	51	1.1×10^2
9[b]	**5a**	17.0	98.3	8.5	15	1.3×10^2
10[c]	**4a**	89.6	96.4	5	48	1.7×10^2
11[c]	**5a**	48.4	99.1	12	33	3.4×10^2
12[c]	**5b**	80.4	99.1	7	45	5.2×10^2
13[c]	**5c**	56.6	98.2	8.5	37	2.0×10^2
14[c]	**5d**	70.5	95.2	7	43	88
15[c]	**5e**	98.7	97.4	6.5	50	3.9×10^2

[a] Averages of duplicate runs. [b] General conditions: 0.2 M substrate, 0.75 equiv $(i\text{-PrCO})_2O$, 0.75 equiv *i*-Pr_2NEt, 4 mol % (*R*)-**3**, Na_2SO_4, $CHCl_3$, rt. [c] General conditions: 0.2 M substrate, 1.5 equiv $(i\text{-PrCO})_2O$, 0.75 equiv *i*-Pr_2NEt, 8 mol % (*R*)-**3**, Na_2SO_4, $CHCl_3$, rt.

at room temperature in chloroform with selectivity factors 2.5 to 27(!) times higher than those obtained with ***2***.[13]

We were finally able to resolve substrate **6c** with high enantioselectivity, taking advantage of its improved solubility under these conditions (entry 8). This compound has previously served as an intermediate in a concise racemic synthesis[13] of cytoxazone (**6d**), a naturally occurring oxazolidinone possessing cytokine modulating activity.[14] BTM-catalyzed KR of *gem*-dimethyl substituted substrates, **5a**−**e**, proceeded more slowly than that of their unsubstituted counterparts **4a**−**e** (cf., e.g., entries 1 and 9). In most of these cases, high conversions were obtained on a convenient time scale by doubling the catalyst and the anhydride loadings (entries 10−15). Efficacy of both Cl-PIQ and BTM catalysts on preparative scale was confirmed experimentally.[15]

In conclusion, we have achieved for the first time kinetic resolution of chiral 2-oxazolidinones via catalytic, highly enantioselective N-acylation. Besides providing a convenient route to these compounds in enantiopure form, these findings pave the way for further exploration of enantioselective N-acylation of other classes of chiral secondary amides. Studies in this direction are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and NMR spectra. These materials are available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) KR of 0.814 g of (±)-**5c** with Cl-PIQ produced 40% isolated yield of the N-acylated product with 92.1% ee, 48% recovered SM with 75.6% ee ($C_{HPLC} = 45\%$, $s = 56$) and 79% recovered catalyst. (b) KR of 1.00 g of (±)-**4e** with BTM gave 51% isolated yield of the product with 96.7% ee, 48% recovered SM with 99.4% ee ($C_{HPLC} = 51\%$, $s = 3.5 \times 10^2$) and 60% recovered catalyst. (c) KR of 0.753 g of (±)-**6c** with BTM gave 48% isolated yield of the product with 91.3% ee, 44% recovered SM with 97.3% ee ($C_{HPLC} = 52\%$, $s = 94$) and 62% recovered catalyst. See experimental details in Supporting Information.

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