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Kinetic Resolution of *N*-Acyl-Thiolactams via Catalytic Enantioselective Deacylation

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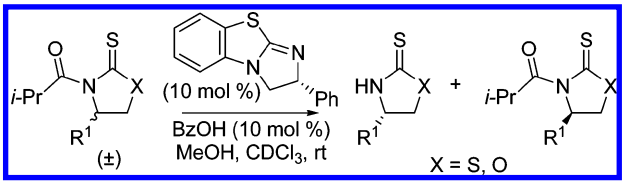
ABSTRACT



Methanolysis of *N*-acyl-thiazolidin-2-thiones and -oxazolidin-2-thiones in the presence of acyl transfer catalyst benzotetramisole (BTM) proceeds in a highly enantioselective fashion thus enabling kinetic resolution of these substrates.

Enzymatic resolution of racemic alcohols, thiols, and amines is routinely accomplished via two basic approaches: (a) enantioselective acylation and (b) enantioselective hydrolysis of the corresponding acylated derivatives. Often, these complementry transformations can be catalyzed by a single enzyme, which, as expected, exhibits the same sense of enantioselection in both directions of the process and thus can be used to achieve *opposite* overall enantioselectivities (see, e.g., Figure 1).

Over the past two decades, considerable progress has been made in the development of nonenzymatic asymmetric acylation catalysts, which can now be used to resolve the aforementioned classes of substrates with good enantioselectivity.[1] However, to our knowledge, there have been no reports of these catalysts being able to operate in reverse and achieve *enantioselective deacylation*.[2−6] In this letter, we disclose the first instances of this transformation.

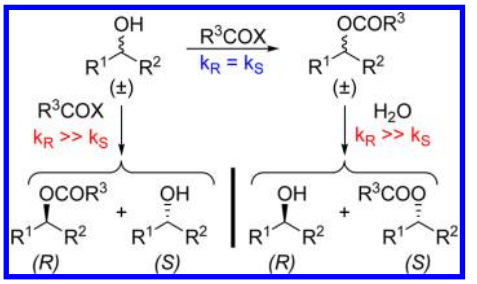


Figure 1. Enzymatic esterification and ester hydrolysis.

In the course of our recent studies on enantioselective N-acylation of lactams and thiolactams,[7,8] we subjected (±)-4-phenylthiazolidine-2-thione **1** to our standard kinetic resolution protocol, which calls for quenching the reaction mixture with methanol to destroy excess anhydride (Figure 2, eq 1). We noted that the enantiomeric excess of the product

(1) For recent reviews, see: (a) Krasnov, V. P.; Gruzdev, D. A.; Levit, G. L. *Eur. J. Org. Chem.* **2012**, 1471. (b) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (d) Spivey, A. C.; Arseniyadis, S. *Top. Curr. Chem.* **2010**, *291*, 233.

(2) (a) The only previously known nonenzymatic enantioselective deacylation was achieved via CBS reduction of *N*-acyl-oxazolidinones and -imidazolidinones: Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1998**, *39*, 6317. (b) In addition, an unsuccessful attempt at enantioselective ester deacylation ($s \leq 1.5$) has been recorded: Yoshizumi, T.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1253.

(3) We use the term "enantioselective deacylation" to describe a reaction in which a racemic acyl donor loses an achiral acyl group to produce a *chiral leaving group* in enantioenriched form (cf. the right-hand side of Figure 1). By contrast, there are many examples of enantioselective alcoholysis (or esterification) of racemic acyl donors wherein *the chirality resides in the acyl group*, while the leaving group (if any) is achiral. See, e.g., refs 4−6.

(4) For select examples of conventional kinetic resolution (KR) of acyl donors via nonenzymatic alcoholysis, see: (a) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187. (b) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466. (c) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230. (d) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (e) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629. (f) Yang, X.; Birman, V. B. *Chem.—Eur. J.* **2011**, *17*, 11296. (g) Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902.

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and the unreacted starting material diminished considerably if the quenched mixture was allowed to stand for too long. As a result, the conversion and the apparent selectivity factor calculated from these parameters[9] plummeted as well.

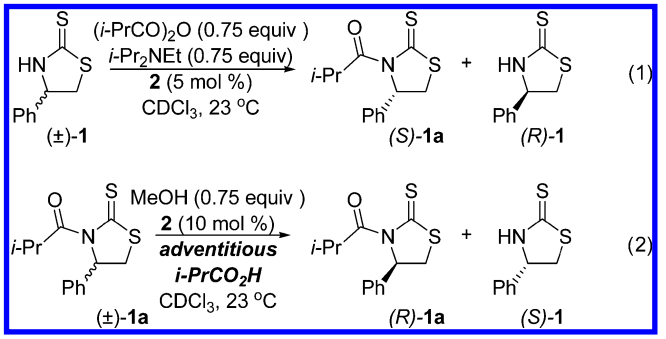


Figure 2. Enantioselective N-acylation of (±)-**1** and the reverse reaction.

We were aware of prior literature reports describing DMAP-catalyzed alcoholysis of *N*-acyl-oxazolidine-2-thione and *N*-acyl-thiazolidine-2-thiones.[10,11] Thus, we quickly realized that we were witnessing an enantioselective version of this process catalyzed by our asymmetric acyl transfer catalyst benzotetramisole (BTM) **2** (Figure 3). To confirm our hypothesis, we subjected racemic **1a**, the *N*-isobutyryl derivative of **1**, to methanolysis under similar conditions. Pleasingly, the reaction yielded the same products with the opposite selectivity and a better selectivity factor than the original "forward" process (eq 2). As expected, in the absence of added catalyst, the methanolysis proceeded at a negligible rate (Table 1, entry 1).

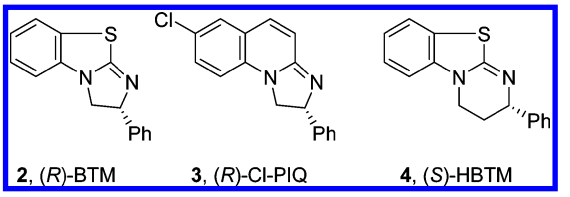
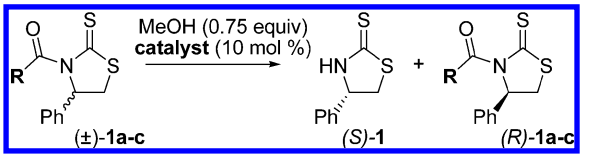


Figure 3. Catalysts used in this study.

Table 1. Optimization Study[a]



entry	catalyst	R	solvent	time	conv %	*s*
1	none	*i*-Pr	$CDCl_3$	7 d	<10	ND[d]
2	**2**	*i*-Pr	$CDCl_3$	4 d	55	26
3	**2**+BzOH	*i*-Pr	$CDCl_3$	24 h	48	78
4[b]	**2**+BzOH	*i*-Pr	$CDCl_3$	24 h	49	81
5[c]	**2**+BzOH	*i*-Pr	$CDCl_3$	24 h	50	84
6	**2**+BzOH	Et	$CDCl_3$	12 h	57	15
7	**2**+BzOH	Ph	$CDCl_3$	7 d	<10	ND[d]
8	**3**+BzOH	*i*-Pr	$CDCl_3$	7 d	37	6.7
9	**4**+BzOH	*i*-Pr	$CDCl_3$	3 d	47	7.0
10	**2**+BzOH	*i*-Pr	CD_2Cl_2	24 h	49	41
11	**2**+BzOH	*i*-Pr	PhMe	24 h	47	86
12	**2**+BzOH	*i*-Pr	Et_2O	7 d	42	3.9

[a] General conditions (0.1 mmol of (±)-**1a**–**c**, 0.075 mmol of MeOH, 0.01 mmol of (*R*)-**2**, 0.01 mmol of benzoic acid, 0.75 mL of solvent, rt) were used, unless specified otherwise. [b] 0.75 equiv of $PhCH_2OH$ was used instead of methanol. [c] 0.75 equiv of $(1\text{-naphthyl})_2CHOH$ was used instead of methanol. [d] Not determined.

It is also noteworthy that the reaction worked only poorly when a thoroughly purified sample of **1a** was used (Table 1, entry 2). Evidently, the traces of isobutyric acid in crude **1a** played the role of a cocatalyst. With the addition of benzoic acid (Table 1, entry 3), the reaction protocol became reproducible and a brief optimization study was undertaken. Benzyl alcohol and di-(1-naphthyl)methanol (Table 1, entries 4 and 5) produced virtually the same results as did methanol. *N*-Propionyl derivative **1b** underwent methanolysis considerably faster than did **1a**, but with greatly diminished enantioselectivity (Table 1, entry 6). Its *N*-benzoyl counterpart **1c** was essentially unreactive (Table 1, entry 7). These results were in line with the observations made in the

(5) For select examples of dynamic kinetic resolution (DKR) of acyl donors via nonenzymatic alcoholysis, see: (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Mastsuda, K.; Formisano, R.; Chaplin, D. A. *Tetrahedron* **1997**, *53*, 7539. (b) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154. (c) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870. (d) Berkessel, A.; Cleeman, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem.* **2005**, *44*, 807. (e) Lu, G.; Birman, V. B. *Org. Lett.* **2011**, *13*, 356. (f) Yang, X.; Birman, V. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 5553.

(6) For select examples of desymmetrization of prochiral *meso*-anhydrides, see: Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

(7) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605.

(8) For examples of nonenzymatic enantioselective N-acylation of other classes of substrates, see: (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. (b) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (c) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870. (d) Binanzer, M.; Hsieh, S. Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698.

(9) (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Enantioselectivity in KR is expressed in terms of a selectivity factor (s) defined as the ratio of reaction rates of the fast- and the slow-reacting enantiomers of the starting material: $s = k_{fast}/k_{slow}$. In the KR of racemic mixtures, it is usually calculated from the ee values of the product and the unreacted starting material according to Kagan's equations (ref 5): (1) conversion $C = ee_{SM}/(ee_{SM} + ee_{PR})$. (2) Selectivity factor $s = \ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$.

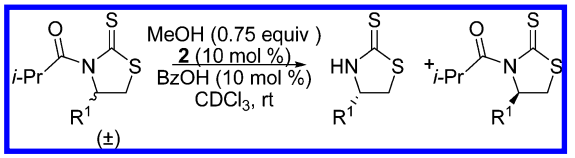
(10) (a) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197. (b) Wu, Y.; Sun, Y.-P.; Yang, Y.-Q.; Hu, Q.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6141.

(11) For reviews of synthetic utility of thiazolidine-2-thiones and oxazolidine-2-thiones, see: (a) Velázquez, F.; Olivo, H. F. *Curr. Org. Chem* **2002**, *6*, 1. (b) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604.

(12) (a) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (b) Yang, X.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2011**, *13*, 4755.

course of our earlier N-acylation studies.[7,12] More surprisingly, much lower reaction rates and selectivity factors were obtained with two other amidine-based catalysts, **3** and **4**, that previously showed good enantioselectivities (Table 1, entries 8 and 9). Among the solvents examined (see Table 1, entries 3 and 10−12), toluene proved to be equal, or even slightly superior, to chloroform. However, for the sake of convenient NMR monitoring, we continued using $CDCl_3$ for the rest of this study. Variation of the aryl substituent suggested that electron-donating groups increase the enantioselectivity, while electron-withdrawing ones diminish it (Table 2, entries 1 and 2 vs 3 and 4). Somewhat surprisingly, replacing the phenyl group with 1- or 2-naphthyl or 2-thienyl was also detrimental (Table 2, entries 5−7), even though the same groups were typically associated with higher levels of enantioselectivity in our previous studies on N-acylation.

Table 2. KR of *N*-Isobutyryl-thiazolidine-2-thiones[a]



entry	R^1	time, d	conv %	*s*
1	*p*-$MeOC_6H_4$ (**5a**)	1	49	90
2	*o*-$MeOC_6H_4$ (**6a**)	1	47	108
3	*p*-ClC_6H_4 (**7a**)	0.6	54	23
4	*o*-ClC_6H_4 (**8a**)	1	50	36
5	1-naphthyl (**9a**)	5	48	30
6	2-naphthyl (**10a**)	2	57	37
7	2-thienyl (**11a**)	1.5	45	32
8	*trans*-Ph-CH=CH (**12a**)	1	47	37
9	CO_2Me (**13a**)	0.6	49	15
10	*i*-Pr (**14a**)	7	0	ND
11	$PhCH_2$ (**15a**)	7	27	1.4
12	— (cf. **16a**, Figure 4)	7	33	2.3

[a] General conditions were used (see Table 1).

Nonetheless, the selectivity factors obtained in these less favorable cases are still amply sufficient for practical purposes ($s > 20$). The styryl group containing an extended π-system also produced a good result (Table 2, entry 8). Diminished enantioselectivity was obtained with the ester-substituted substrate (Table 2, entry 9). No reaction was observed with the isopropyl group lacking a π-system (Table 2, entry 10). Similarly, extremely a low reaction rate and enantioselectivity were observed in the case of the 4-benzyl-substituted substrate (Table 2, entry 11), wherein the π-system is one atom farther away from the nitrogen. These negative results were fully consistent with our earlier N-acylation studies and once again underscored the importance of π-interactions in the transition state.[7] On the other hand, we were disappointed to observe the slow conversion and the low selectivity factor in the case of the indane-fused substrate **16a**, in which the benzene ring is geometrically constrained (Table 2, entry 12). Similarly poor results were also obtained in the reverse direction: acylation of (±)-**16** (Figure 4). These results were in contrast with the successful enantioselective N-acylation of the

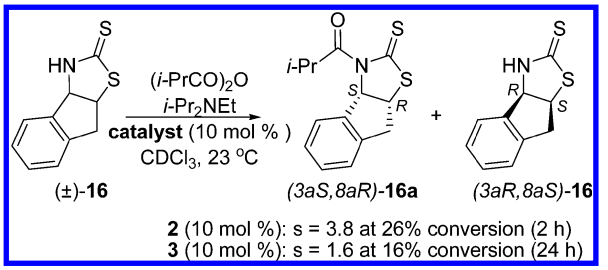
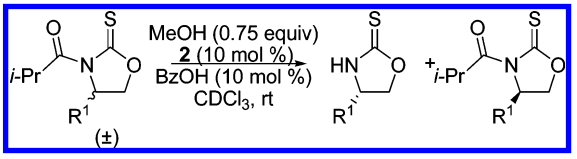


Figure 4. Enantioselective N-acylation of (±)-**16**.

structurally similar indane-fused oxazolidin-2-one and β-lactam in the presence of Cl-PIQ **3** (selectivity factors 36 and 14 were obtained, respectively).

Alcoholysis of the analogous *N*-isobutyryl-oxazolidin-2-thiones was examined next (Table 3). The reaction proved to be rather slow, but still afforded synthetically useful levels of enantioselectivity in most cases.[13] Significantly, we observed that the apparent enantioselectivity of deacylation of the ester-substituted substrate **22a** diminished with time (Table 3, entries 6 and 7). We surmised that the deacylated product (*R*)-**22** may undergo slow acyl group exchange with the unreacted (*S*)-**22a** under the reaction conditions. By the same token, gradual racemization should also be observed during enantioselective acylation of (±)-**22** in the presence of BTM **2**. A control experiment confirmed that this is indeed the case (Table 4). The reaction reached essentially complete conversion within 30 min. HPLC analysis of the crude mixture indicated significant enantiomeric enrichment of both the product and the starting material corresponding to a selectivity

Table 3. KR of *N*-Isobutyryl-oxazolidine-2-thiones[a]

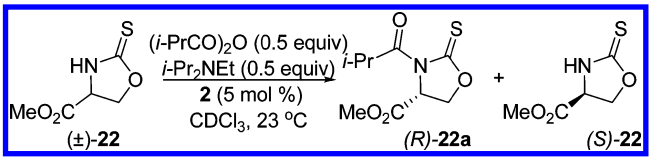


entry	R^1	time, d	conv %	*s*
1	phenyl (**17a**)	2	36	57
2	*p*-$MeOC_6H_4$ (**18a**)	4	47	59
3	*o*-$MeOC_6H_4$ (**19a**)	6	30	38
4	*p*-ClC_6H_4 (**20a**)	3	57	13
5	*o*-ClC_6H_4 (**21a**)	3	43	32
6	CO_2Me (**22a**)	4	53	2.6
7	CO_2Me (**22a**)	1	29	7.9

[a] General conditions were used (see Table 1).

(13) The analogous *N*-acyloxazolidin-2-ones do not react under these conditions. Resolution of racemic oxazolidinones is thus best achieved via enantioselective acylation, as previously described.[7,12a]

Table 4. Enantioselective N-Acylation of (±)-**22**[a]



entry	time, h	(*R*)-**22a**, ee %	(*S*)-**22**, ee %	conv %	*s*
1	0.5	75	82	52	17
2	1.0	57	62	48	7.5
3	2.3	39	47	54	3.5
4	8.0	33	36	52	2.8
5	48	3.0	3.8	56	1.1

[a] Single data points are presented for the sake of consistency. For duplicate results, see Supporting Information.

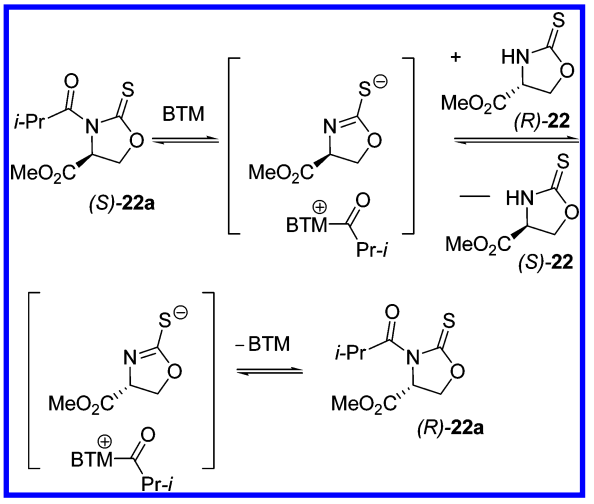


Figure 5. Racemization of **22** and **22a** via acyl exchange.

factor of 17. However, the ee's dropped significantly over the next 2 h leading to diminished apparent selectivity factors. We hypthesized that the acyl group exchange is likely to be promoted by BTM, via the acyl transfer mode of catalysis (Figure 5).

Table 5. Racemization of **22** and **22a**[a]

		ee % after 24 h	
entry	catalyst	(*R*)-**22a**	(*S*)-**22**
1	none	81	77
2	**2** (10 mol %)	18	14
3	**2**+ BzOH (10 mol % each)	20	11
4	*i*-Pr_2NEt (50 mol %)	81	74
5	*i*-$PrCO_2H$ (10 mol %)	82	75

[a] Conditions: 0.1 M (*R*)-**22a** (ee = 82%) and 0.1 M (*S*)-**22** (ee = 78%) in $CDCl_3$, 10 mol % catalyst, rt, 24 h.

Indeed, when we mixed roughly equimolar amounts of enantioenriched (*R*)-**22a** and (*S*)-**22** in the presence of 10 mol % (*R*)-BTM **2**, both ee values deteriorated significantly over the course of 24 h, whether or not benzoic acid was also added (Table 5, entries 2 and 3). In contrast, the ee's remained virtually unchanged in the absence of additives or in the presence of Hünig's base or isobutyric acid (Table 5, entries 1, 4, and 5). Taken together, these results clearly demonstrate the reversibility of the deacylation of **22a**, which explains the low apparent selectivity factors in Table 3, entries 6 and 7. The same racemization pathway probably also operates to some extent in the case of other substrates reported in this study, particularly when the reaction times are long. Thus, the experimentally observed *s*-values shown in Tables 2 and 3 are likely to be lower than the "true" enantioselectivities.

In conclusion, we have demonstrated for the first time the possibility of catalytic enantioselective deacylation promoted by an acyl transfer catalyst. At present, this methodology provides an alternative means of achieving kinetic resolution of thiazolidine- and oxazolidine-2-thiones. Other applications will be reported in due course.

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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.

The authors declare no competing financial interest.