Communication

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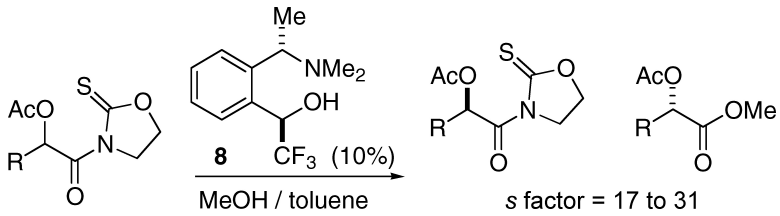

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Kinetic Resolution of α-Acetoxy *N*-Acyl Oxazolidinethiones by a Chiral O-Nucleophilic Acyl Transfer Catalyst

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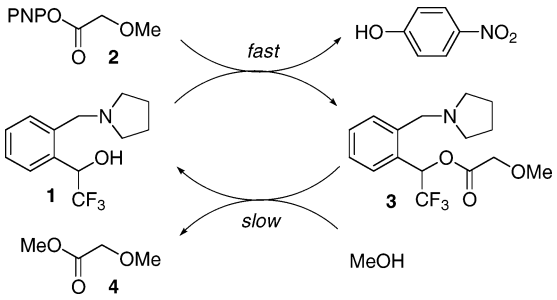
We recently described a series of catalysts bearing a hydroxyl group in close proximity to a basic amine which effect the methanolysis of *para*-nitrophenyl (PNP) esters.[1a] These catalysts, an example of which is provided in Scheme 1, operate by an O-nucleophilic mechanism in which the hydroxyl group of the catalyst (**1**) undergoes base-catalyzed acylation by the PNP ester (**2**) to give the acylated intermediate (**3**). This intermediate then undergoes base-catalyzed deacylation to provide the product (**4**) and regenerate the catalyst (**1**). In the course of our studies, we found that the deacylation step of the catalytic cycle is turnover-limiting, and that catalysts containing alcohols with a proximal electron-withdrawing group are more active, probably due to their enhanced leaving group ability. The catalysts we studied are chiral, and in this communication, we describe the use of two such catalysts for the kinetic resolution of chiral α-acetoxy oxazolidinethione imides.[2,3]

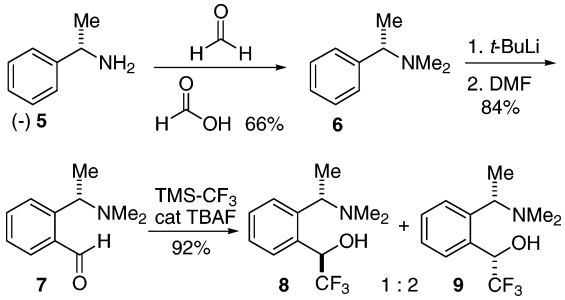
In considering the synthesis of asymmetric catalysts for this process, we wished to avoid any resolution steps and, therefore, sought chiral, nonracemic starting materials. Catalysts derived from α-methylbenzylamine (**5**, Scheme 2) seemed particularly attractive in this regard since both enantiomers of this material are available in nonracemic form for about $1/gram.[4] This compound was used as our starting material and required conversion of the primary amine to a tertiary amine and incorporation of a β-trifluoroethanol group. Toward this end, subjection of (−)-**5** to Eschweiler−Clarke methylation provided dimethylamine **6**[5] in 66% yield, and directed ortho-metalation with *t*-BuLi and trapping with DMF provided aldehyde **7** in 84% yield. Trifluoromethylation of **7** according to the Olah−Prakash procedure[6] proceeds in 92% yield to provide a 1:2 mixture of **8** and **9**, which are easily separable by flash chromatography and which were unambiguously distinguished by X-ray crystallography. This three-step sequence proceeds in 51% overall yield and affords ready access to either enantiomer of **8** or **9**.

With catalysts **8** and **9** in hand, we first studied the methanolysis of various α-siloxy PNP esters. Several substrates were examined in a variety of solvents. However, in all cases, the reactions proceeded with modest levels of selectivity. The highest selectivity factor (*s*-factor)[7] observed with catalyst **8** was 2.8, while with catalyst **9**, it was 1.6. Furthermore, catalyst **8** was consistently more active than catalyst **9** by a factor of about 3. We wished to increase the selectivity of this process and considered the flexibility of our substrate a detriment. A more rigid substrate would present a more defined topography to the catalyst, and we, therefore, turned our attention to the *N*-acyl oxazolidinethione derivatives shown in Figure 1. The thiocarbonyl unit of these compounds is highly polarized, and it likely exists in a dipole-minimized conformation anti to the *N*-acyl carbonyl. This introduces a significant amount of A[1,3]-strain at the α-carbon and a preference for the conformation

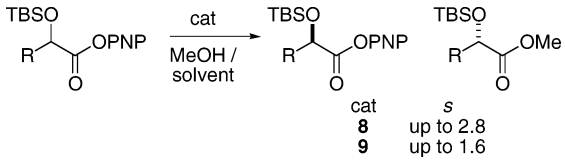
Scheme 1. O-Nucleophilic Acyl Transfer Catalysts



Scheme 2. Synthesis of Nonracemic Catalysts



Scheme 3. Methanolysis of *para*-Nitrophenyl Esters



wherein the smallest group, H, is in the most hindered position. This serves as an effective conformational anchor and forces the alkoxy groups to point in opposite directions in the enantiomers.

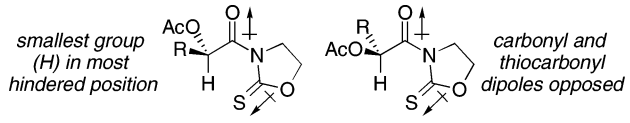


Figure 1. *N*-Acyl oxazolidinethione substrates.

We first studied the activity of catalysts **8** and **9** in the methanolysis of the mandelic acid derived substrate **10** and found that catalyst **9** reacts sluggishly and with low levels of selectivity. Catalyst **8**, however, is much more efficacious, and at 0 °C, promotes the methanolysis of **10** with an *s*-factor of 17 (at 58.5% conversion, starting material is recovered in 94% ee). With this initial success, we next studied the effects of solvent on the rate and selectivity of this process, as shown in Table 1. Of the solvents we studied, the reaction is fastest in CH_2Cl_2, proceeding to 53%

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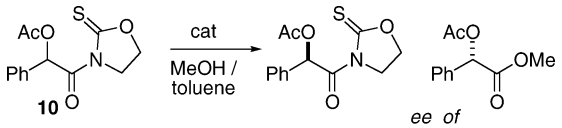
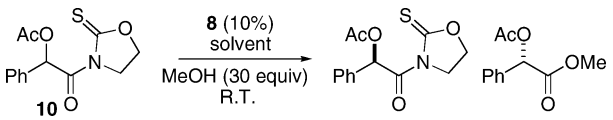
Scheme 4. Methanolysis of *N*-Acyl Oxazolidinethione **10**



cat	Time (h)	% conv	*s*	temp	ee of recovered SM
8	67	59	17	0°C	94%
8	5	55	12	rt	82%
9	43	20	2	rt	--

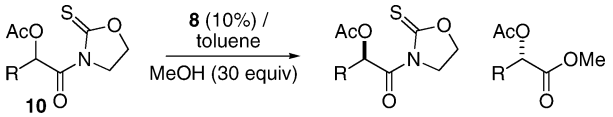
Table 1. Solvent Effects on the Methanolysis of **10**



entry	solvent	time (h)	% conv	*s*-factor
1	toluene	5	55	12
2	toluene/EtOH (30 equiv)[a]	24	46	12
3	CH_2Cl_2	2	53	9
4	THF	19	55	5
5	*t*-amyl alcohol/CH_2Cl_2 (1:1)	8	48	11
6	EtOH/THF (2:1)[a]	7	37	8.5

[a] Methanol was omitted from this reaction, thereby providing the ethyl ester.

Table 2. Substrate Scope (average of two runs)



entry	R	temp (°C)	time (h)	% conv	ee of recovered SM	*s*
1	Ph (**10**)	0	67	58.5	94%	17
2	Bn (**11**)	0	55	58.8	>99%	31
3[a]	Bn (**11**)	0	120	58.9	>99%	32
4	$PhCH_2CH_2$ (**12**)	0	93	58.5	96%	20
5	Bu (**13**)	0	116	56.4	96%	27
6	*i*-Pr (**14**)	rt	168	58.3	96%	20
7	allyl (**15**)	−25	168	54.6	91%	22

[a] This run was conducted with 5% catalyst loading.

conversion in 2 h (Table 1, entry 3). However, the *s*-factor in this solvent is 9, lower than that in toluene. In THF, the reaction is significantly slower, requiring 19 h to proceed to 55% conversion, and provides an eroded *s*-factor of 5 (Table 1, entry 4). We wished to study the use of hydroxylic solvents; however, the background reaction is too great in methanol, and compound **10** is only sparingly soluble in *t*-amyl alcohol or ethanol. It is soluble in a 1:1 mixture of *t*-amyl alcohol and CH_2Cl_2 or a 2:1 mixture of ethanol and THF. These solvent systems proved inferior to toluene, providing diminished *s*-factors of 11 and 8.5, respectively, at about half the rate (Table 1, entries 5 and 6).

Having established that toluene is the solvent of choice, we next studied the scope of this reaction and found that a variety of substrates are effectively resolved (Table 2). Thus, the benzyl- (**11**) and dihydrocinnamyl (**12**)-derived substrates react with *s*-factors of 31 and 20, respectively (entries 2 and 4). Simple alkyl-derived substrates, such as butyl (**13**) and isopropyl (**14**), also display good *s*-factors (27 and 20, respectively, entries 5 and 6). Finally, the allyl-derived substrate (**15**) reacted with an *s*-factor of 22 (entry 7).

While the turnover-limiting step of the catalytic cycle is likely the deacylation of an acyl catalyst intermediate analogous to **3**,[1a] the stereochemistry-determining step is the acylation of the catalyst. Several stoichiometric[8] and catalytic[9] stereoselective acylations of chiral alcohols are known; however, we do not have sufficient understanding of the factors that govern the stereoselectivity of such processes to propose a stereochemical model for our system.

In conclusion, we have described a new method for the kinetic resolution of α-acetoxy *N*-acyl oxazolidinethiones using a readily prepared catalyst. The reaction has a wide substrate scope and provides material of high enantiomeric excess. Efforts to apply this catalyst to the kinetic resolution of other substrate classes are in progress.

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Note Added after ASAP Publication. Typographical errors in the second paragraph and ref 3 were corrected after this paper was published on the Internet on September 7, 2005.

Supporting Information Available: Experimental procedures for the synthesis and characterization of all new compounds, as well as ^1H and ^{13}C spectra for selected compounds, and X-ray crystallography data for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The price listed in the 2004−2005 Acros Organics catalogue for the D-(+) and L-(−) enantiomers of **5** (each 99% ee) is $119.40 and $114 per 100 grams, respectively.

(5) This compound is also commercially available, but at higher cost (Acros Organics price is $35 or $49/g for the (−)- and (+)-enantiomers, respectively).

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