Dynamic Kinetic Resolution

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Nonenzymatic Dynamic Kinetic Resolution of α-(Arylthio)- and α-(Alkylthio)alkanoic Acids**

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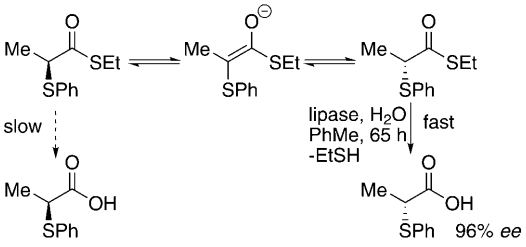
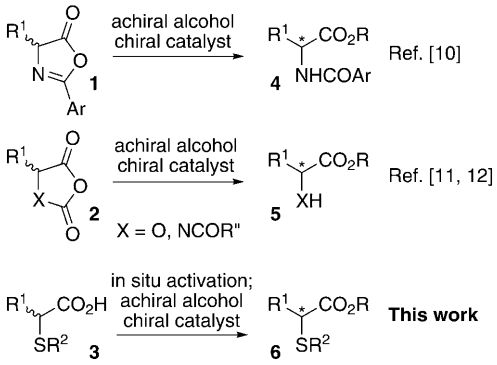
α-(Arylthio)- and α-(alkylthio)alkanoic acids and their derivatives are widely used in drug design.[1] Compounds of this class are also valuable as synthetic intermediates.[2] Both of these considerations underscore the importance of their availability in nonracemic form. Their synthesis from enantioenriched α-halo- or α-(sulfonyloxy)alkanoic acids[1b,2b] by the nucleophilic displacement of the leaving groups, although effective, is dependent upon the availability of suitable chiral precursors. Methods based on the asymmetric generation of the stereogenic center in α-(arylthio)- and α-(alkylthio)alkanoic acids and their derivatives are restricted in their scope.[3] Given the ease of preparation of the corresponding racemates[2] resolution-based approaches have certain advantages. Compared to classical resolution[4,5] and kinetic resolution (KR),[6,7] dynamic kinetic resolution (DKR),[8] which converts both enantiomers of the starting material into one enantiomer of the product, is especially attractive. The DKR protocol disclosed by Drueckhammer and co-workers[9] was successfully applied to (±)-α-(phenylthio)propanoic acid and relies on enzymatic hydrolysis of the corresponding ethyl thioester, which undergoes rapid racemization under the reaction conditions (Scheme 1). Its only obvious drawbacks are the need to handle malodorous ethanethiol and the fact that the requisite enzyme is available in only one enantiomeric form, therefore the reversal of the enantioselectivity of the reaction would require identification of a different enzyme and a different set of reaction conditions.



Scheme 1. Enzymatic DKR of thioesters.[9]

Herein, we report the first examples of the direct DKR of α-(arylthio)- and α-(alkylthio)alkanoic acids by enantioselective esterification promoted by small-molecule catalysts. To the best of our knowledge, enantioselective, nonenzymatic DKR has so far been achieved for only two types of activated carboxylic acid derivatives: azlactones **1**[10] and cyclic carboxyanhydrides **2**[11,12] (Scheme 2).[13]



Scheme 2. Chiral acyl donors amenable to nonenzymatic DKR.

In the course of our recent studies[7c] on KR of α-substituted alkanoic acids catalyzed by homobenzotetramisole ((*S*)-HBTM, **7**; Figure 1),[14a] we observed that the unreacted α-(phenylthio)propanoic acid was recovered with an unexpectedly low *ee* value when the reaction was carried out at room temperature (Scheme 3). We realized that this result must be due to in situ racemization of the less-reactive enantiomer of the substrate. Given the inherently higher efficiency of DKR compared to conventional KR, we sought to optimize the newly discovered process.

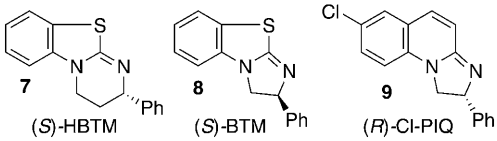


Figure 1. The catalysts used in this study.

In the context of KR, it was sufficient to activate only half of the substrate. Therefore, our standard KR protocol relied on the in situ conversion of the racemic acid into its symmetrical anhydride by treatment with 0.53 equivalents of

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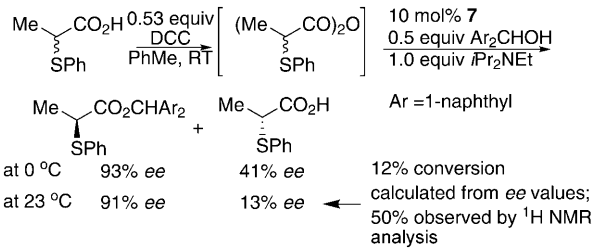
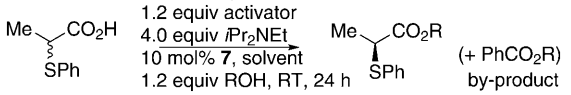


Scheme 3. Evidence of in situ racemization during KR. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

DCC. For DKR we needed to generate stoichiometric amounts of the chiral acyl donor. The use of 1.2 equivalents of DCC produced the ester with a high *ee* value, but the reaction was slow and accompanied by the formation of side products (Table 1, entry 1). Pivalic anhydride[15b] reacted more cleanly, but the reaction was also slow (Table 1, entry 2). Fortunately, the use of benzoic anhydride, which is

Table 1: Variation of the DKR protocol.



Entry	Activator	Solvent	ROH	Yield [%][a]	*ee* [%]
1	DCC	[D8]PhMe	1-Np2CHOH	35	89
2	Piv2O	[D8]PhMe	1-Np2CHOH	35	91
3	Bz2O	[D8]PhMe	1-Np2CHOH	91	91
4[b]	Bz2O	[D8]PhMe	1-Np2CHOH	49	−84
5[c]	Bz2O	[D8]PhMe	1-Np2CHOH	87	46
6	Bz2O	CD_2Cl_2	1-Np2CHOH	67	79
7	Bz2O	$CDCl_3$	1-Np2CHOH	61	84
8	Bz2O	C_6D_6	1-Np2CHOH	88	87
9	Bz2O	[D8]THF	1-Np2CHOH	66	88
10	Bz2O	CD_3CN	1-Np2CHOH	60	46
11	Bz2O	[D8]PhMe	Ph2CHOH	97	83
12	Bz2O	[D8]PhMe	$PhCH_2OH$	93	26
13	Bz2O	[D8]PhMe	1-$NpCH_2OH$	99	15
14	Bz2O	[D8]PhMe	2-$NpCH_2OH$	94	20
15	Bz2O	[D8]PhMe	*i*PrOH	89	49

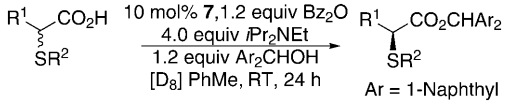
[a] Determined by ^{1}H NMR analysis. [b] Catalyst **8** was used instead of **7**. [c] Catalyst **9** was used instead of **7**. For structures of **7**, **8**, and **9** see Figure 1. Bz = benzoyl, Np = naphthyl, Piv = 2,2-dimethylpropanoyl, THF = tetrahydrofuran.

employed in Shiina's original protocol for the BTM-catalyzed KR of arylpropanoic acids,[15a] proved to be optimal. Within 24 hours, the desired ester was obtained in 91% yield with 91% *ee*, accompanied by approximately 9% of the benzoate ester by-product (Table 1, entry 3).

Variation of other reaction parameters was undertaken next. (*S*)-HBTM (**7**; Figure 1; Table 1, entry 3) was superior to (*S*)-BTM[14b] (**8**; entry 4) and (*R*)-Cl-PIQ[14c] (**9**; entry 5), a result that is in agreement with our earlier study.[7c] Several additional solvents were tested and they all produced somewhat lower *ee* values and yields than toluene (Table 1, entries 6–10). Although di(1-naphthyl)methanol (Table 1, entry 3), originally identified by Shiina et al.[15a] and subsequently used in our studies,[7c,10f] once again proved to be optimal, diphenylmethanol also produced useful levels of enantioselectivity (Table 1, entry 11). Results obtained with primary benzyl alcohols (Table 1, entries 12–14) and isopropanol (entry 15) were less satisfactory.

Having thus established the basic parameters of the new method, we proceeded to explore its substrate scope (Table 2). Electron-donating or electron-withdrawing substituents on the phenyl ring had no appreciable effect on the enantioselectivity (Table 2, entries 2–6). However, replacing

Table 2: Exploration of the substrate scope.[a]



Entry	R^1	R^2	By-product [%][b]	Yield [%][c]	*ee* [%]
1	Me	Ph	9	90	91
2	Me	*p*-MeC_6H_4	6	85	92
3	Me	*p*-$MeOC_6H_4$	8	89	91
4[d]	Me	*p*-$MeOC_6H_4$	n.d.	92	90
5	Me	*p*-ClC_6H_4	5	93	89
6	Me	*p*-BrC_6H_4	4	91	91
7	Me	$PhCH_2$	12	88	85
8	Me	$CH_3(CH_2)_7$	13	87	84
9	Et	Ph	20	62	86
10	*n*Bu	Ph	20	71	86
11	*i*Pr	Ph	38	13[e]	66

[a] Performed on 0.10 mmol (±)-substrate, unless specified otherwise. [b] Yield of the by-product ($PhCO_2CH(1\text{-Np})_2$) was determined by ^{1}H NMR analysis. [c] Yield of isolated product ((96 ± 3)% pure by ^{1}H NMR) unless specified otherwise. [d] Performed on 1.0 mmol scale (see the Experimental Section). [e] Yield was determined by ^{1}H NMR analysis. n.d. = not determined.

the phenyl group with a benzyl or *n*-octyl group proved to be slightly detrimental (Table 2, entries 7 and 8). Replacing the methyl group with a primary alkyl group also led to some loss of enantioselectivity; the reaction proceeded more slowly, thus resulting in lower yields of the desired product and the concomitant increase in the yield of the benzoate ester by-product (Table 2, entries 9 and 10). When a secondary alkyl substituent was introduced, the benzoate ester became the predominant product (Table 2, entry 11).

We confirmed that both the lithium aluminum hydride reduction and the trifluoroacetic acid catalyzed deprotection of the DKR products occur in high yield (95% and 85%, respectively) and without any loss of stereochemical integrity. In the former reaction, di(1-naphthyl)methanol was also recovered in 90% yield.

In conclusion, we have developed the first nonenzymatic, enantioselective method for the DKR of α-(arylthio)- and α-(alkylthio)alkanoic acids. In contrast to the existing enzymatic protocol, it neither requires the prior conversion of the substrates into their thioesters nor releases ethanethiol in the course of the reaction, and can be directed towards either enantiomer of the product simply by switching the absolute configuration of the catalyst. Extension of the new DKR process to other classes of acyl donors is under investigation and will be reported in due course.

Experimental Section

General procedure: Racemic α-(*p*-methoxyphenylthio)propanoic acid (212 mg, 1.00 mmol), *i*Pr_2NEt (0.70 mL, 4.0 mmol), and benzoic anhydride (280 mg, 1.20 mmol) were dissolved in 10 mL of toluene. The resulting mixture was stirred at room temperature for 5 min and then treated sequentially with (*S*)-HBTM (**7**; 27 mg, 0.10 mmol) and di(1-naphthyl)methanol (340 mg, 1.20 mmol). After 24 h, the reaction mixture was quenched by the addition of benzylamine (0.15 mL, 1.4 mmol), and then placed directly on a silica gel column. Elution with hexanes/ethyl acetate (9:1) gave 440 mg (92% yield) of the desired *S* ester in 89.6% *ee* (99% pure as determined by ^{1}H NMR analysis).

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