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Thiol-Free Multicomponent Synthesis of Non-racemic β-Acyloxy Thioethers from Biocatalytically Obtained Chiral Halohydrins

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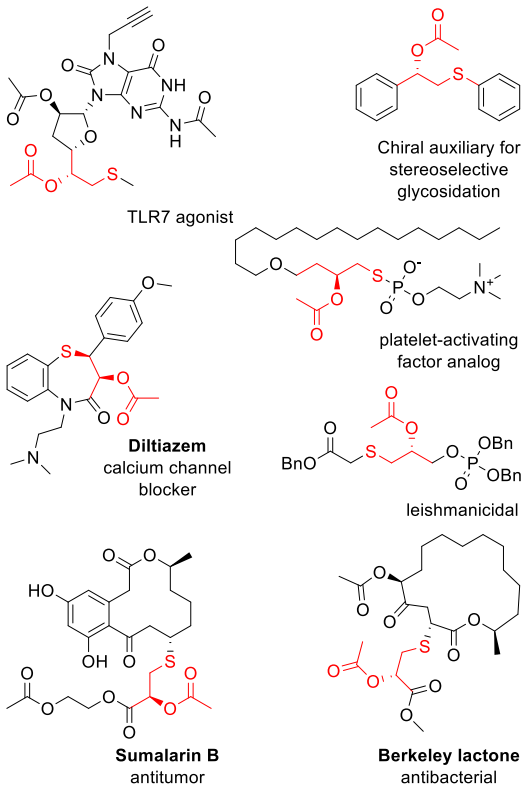
A novel multicomponent chemoenzymatic strategy for the preparation of enantioenriched β-acyloxy thioethers has been developed. This robust methodology employs mild bases, air atmosphere, room temperature and avoids the use of foul-smelling thiols. Instead, potassium thioacetate is employed as a universal sulfur source. This chemoselective strategy tolerates aromatic and aliphatic components and diverse functional groups. The chirality is enzymatically defined by ADH-catalyzed bioreduction of α-haloketones delivering an enantioenriched halohydrin which is one of the three components, and the optical purity remains untouched in the final product. Semipreparative scale multicomponent reaction affords high yield of the products (up to 96%).

Introduction

Multicomponent reactions (MCRs) are defined as transformations that combine at least three reactants in the same pot to generate a product containing most (preferably all) atoms from the starting materials. These reactions are characterized by their high atom economy, and the ability to modulate the substituents in the final product. Through the years, MCRs have become important strategies in the production of molecular diversity.[1,2]

Indeed, the high bond-forming power and robustness of MCRs perfectly match with the exquisite selectivity and reaction mildness displayed by the asymmetric enzymatic reactions. Regarding the combination of biocatalytic reactions and MCR, two main strategies can be surveyed in the recent literature: i) the MCR rendering a racemic (or prochiral) product, which then undergoes enzymatic kinetic resolution (or asymmetric transformation) to deliver the final non-racemic product,[3] and ii) the biocatalytic preparation of an enantioenriched compound that bears the functional group to efficiently participate in the subsequent MCR, thus affording a product that contains the preformed (or even additional) stereocenters. Most examples are related to the second strategy. As biocatalytic reactions have demonstrated outstanding performance in asymmetric synthesis of chiral building blocks, they can be easily run to produce the required chiral input in MCRs. For example, the enzymatic reaction defines one (or more) stereocenter(s) through the formation of an imine (or iminium) that can readily react with an isonitrile and a carboxylic acid to render the Ugi product in high *ee* and *dr*.[4]

Meanwhile, sulfur-containing compounds that exhibit hydroxy or acyloxy derivatives at ß-position to the sulfur atom, are relevant moieties that are present in several important synthetic and natural products (Scheme 1).[5–9]



Scheme 1 Important synthetic and natural ß-acetoxy thioethers

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† *Dedicated to Prof. Alicia B. Peñéñory on the occasion of her retirement.*

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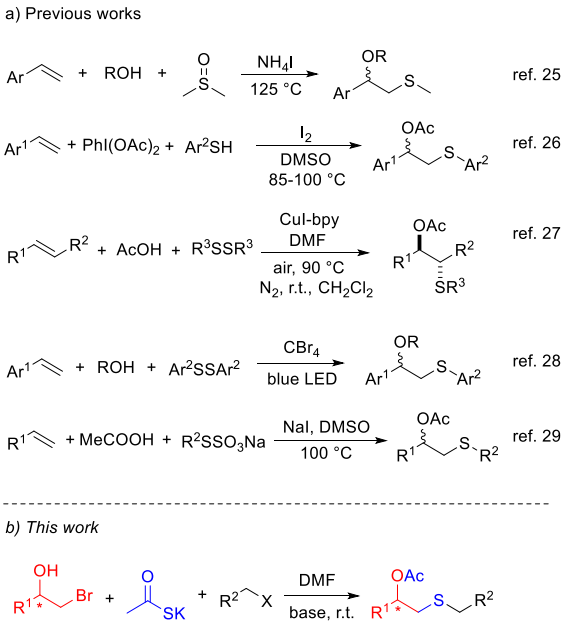
These derivatives show a broad scope of bioactivities and applications such as therapeutic agents, antiasthma, and inhibitors of DNA-topoisomerase, among others.[10] Indeed, some synthetic strategies have been developed for the synthesis of chiral ß-acyloxy thioethers, where most of them involve epoxide[11] o thiirane ring-opening. However, just a few examples of asymmetric procedures have been published to obtain such compounds (Schemes S1-S2, see SI).[12] On the one hand, it is worth mentioning the *meso* epoxide ring-opening using thiols as nucleophiles in the presence of different Lewis acid catalysts, such as metal complexes (Zn,[13] Ga,[14] In,[15] Sc[16]) with chiral ligands (salen, BINOL, tartrate), or chiral phosphates[17,18] (Scheme S1, see SI). Indeed, the use of costly/low abundance metals and chiral ligands is generally expensive. Besides, in certain cases, heavy metals are associated with toxicity issues. Furthermore, the use of thiols is not methodologically convenient, due to their frequent bad smell and their instability toward aerobic oxidation.

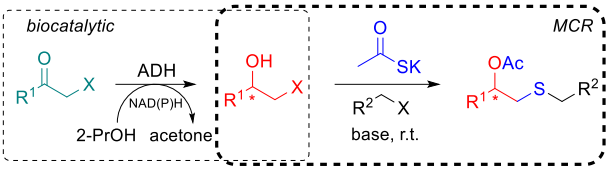
On the other hand, there are examples involving the enantioselective reduction of α-thiocyanate ketones catalyzed by a chiral oxazaborolidine (Corey-Bakshi-Shibata catalyst),[19,20] the reduction of α-sulfenyl-ß-keto esters by *Saccharomyces cerevisiae*[21] and the reduction of α-thiocyanate ketones promoted by *S. cerevisiae* or *M. isabellina*[22] (Scheme S2, see SI). Noteworthy, the use of biocatalysts for the synthesis of ß-hydroxy sulfides or derivatives remains largely underexplored.[23–25]

Particularly, a number of protocols for the synthesis of ß-acyloxy thioethers have been reported in the last 15 years (Scheme 2a). All of them involve alkenes and different sulfur sources, such as dimethylsulfoxide,[26] thiols,[27] disulfides,[28,29] and organic thiosulfates (Bunte salts).[30] Most of such methodologies depend on the use of aromatic reactants, making them unsuitable for the preparation of totally aliphatic target products. Remarkably, the aforementioned protocols do not allow enantiocontrol in the reaction outcome.



Scheme 2 Different methodologies for ß-O-substituted sulfide synthesis.

With this in mind, we envisioned a chemoenzymatic strategy for a thiol-free preparation of chiral non-racemic ß-acyloxy thioethers, based on two premises: 1) biocatalysis may generate enantioenriched chiral inputs that can participate in a three-component reaction,[31,32] and 2) ß-acyloxy thioethers can be obtained in one-pot two-step process by reacting a chiral halohydrin, a thiocarboxylate salt (e.g. potassium thioacetate)[33] and a suitable electrophile in the presence of a mild base (Scheme 3).[34]

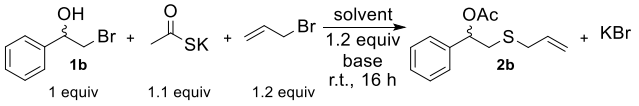


Scheme 3 Chemoenzymatic strategy for the synthesis of non-racemic ß-acyloxy thioethers.

Results and Discussion

Firstly, *rac*-1-bromooctan-2-ol **1a** was tested as substrate for the novel multicomponent reaction, along with potassium thioacetate (solid, easy to handle and fairly stable sulfur source) and 1-(bromomethyl)-2-iodobenzene in DMF and *t*-BuOK as base. Fortunately, a single product was isolated (45%), and its structural elucidation confirmed the corresponding *rac*-ß-acyloxy thioether **2a**. In a first set of experiments, different bases were tested using *rac*-2-bromo-1-phenylethanol **1b** as the substrate (a simple and commercially available halohydrin), potassium thioacetate and allyl bromide as electrophile, in DMF (Table 1).

Table 1 Screening of solvents and bases employing an aromatic halohydrin.[a]



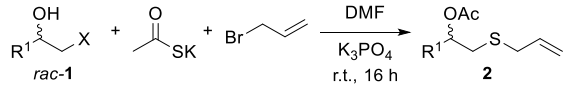
Entry	Solvent	Base	**2b** (%)[b]
1	DMF	K_3PO_4	>99
2	DMSO	K_3PO_4	>99
3	DMF	*t*-BuOK	>99
4	DMSO	*t*-BuOK	>99
5	DMF	Et_3N	-[c]
6	DMF	DMAP	-[c]
7	DMF	Ph_3P	-[c]

[a] Reaction conditions: halohydrin (0.11 mmol), potassium thioacetate (0.12 mmol), allyl bromide (0.13 mmol), base (0.13 mmol), solvent (0.5 mL), air atmosphere, r.t., 16 h. [b] Determined as relative area by GC. [c] Complex mixture.

The here described MCR is operationally simple and air atmosphere is perfectly suitable, as well as ambient humidity at r.t. In a first step, to a solution of the halohydrin, the thiocarboxylate salt was added. After completion of the first S_N2 reaction, the second electrophile and the base were added. The

best results were obtained with a mild base such as K_3PO_4, but a strong one (*t*-BuOK) can also be used (Table 1, entries 1-4). Polar aprotic solvents such as DMF as well as DMSO gave successful reactions. Interestingly, nitrogenous bases (Et_3N and DMAP) and phosphorous bases (Ph_3P), included in the set due to their solubility in organic solvents, rendered a complex mixture of products (Table 1, entries 5-7). This may be partly due to the capability of amines to participate in side-acyl transfer reactions.[35] After setting the optimal conditions, different aromatic and aliphatic halohydrins were examined (Table 2).

Table 2 One-pot synthesis of ß-acyloxy thioethers using alkyl- and aryl halohydrins.



Entry	Substrate	R^1	X	Product	Yield[a]
1	**1b**	Ph	Br	**2b**	75%
2[b,c]	**1b'**	Ph	Cl	**2b**	73%
3[d]	**1c**	*p*-NO_2-Ph	Br	**2c**	50%
4	**1d**	COOEt	Br	**2d**	54% (96%)[e]
5	**1e**	*p*-OMe-Ph	Br	**2e**	56%
6[b]	**1f**	CH_2COOEt	Cl	**2f**	-[f]

[a] Isolated yields. [b] 0.13 mmol **1b'**, 1.1 equiv. potassium thioacetate, 1.2 equiv. allyl bromide and 1.2 equiv. *t*-BuOK. [c] Reaction mixture was heated (60°C) until complete consumption of the halohydrin. [d] (*S*)-**1c** was used instead of *rac*-**1c**. [e] 0.5 mmol **1d**. [f] Complex mixture.

Remarkably, in most cases, after work up, MCR products were obtained with high purity. On the one hand, aryl halohydrins provided the corresponding multicomponent products in good isolated yields (from 50% to 75%). Besides **1b**, 2-chloro-1-phenylethanol **1b'** was also tested. For the latter, higher temperature (60 °C) was needed, but the isolated yield was not affected (75% vs 73%, respectively, Table 2, entries 1 and 2). Likewise, (enantiopure) aryl halohydrins bearing an electron-withdrawing group (EWG) or an electron-donor group (EDG) gave similar good results (50% and 56% isolated yield, respectively) under these reaction conditions (Table 2, entries 3 and 5). Ester-bearing aliphatic halohydrin **1d** was as well accepted, obtaining **2d** in excellent isolated yield (96%, starting from 0.5 mmol **1d**, Table 2, entry 4). Interestingly, when this reaction was conducted at lower scale (0.25 mmol **1d**), 54% isolated yield was obtained, thus emphasizing that conducting the reactions at a higher scale minimize work up-associated mass losses. Notwithstanding, when **1f** was tested, the corresponding product was not obtained (Table 2, entry 6), likely due to enolate anion formation that can lead to a complex mixture of products after the addition of the electrophile.

Subsequently, different electrophiles: alkyl halides bearing ester, alkyne, alkene, alkyl, and benzyl moieties, and *n*-butyl acrylate ester, were examined toward aromatic and aliphatic halohydrins (Table 3).

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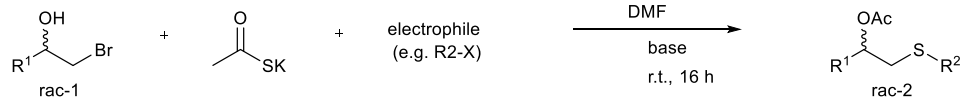
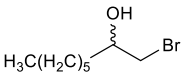
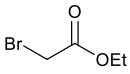
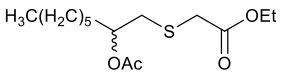
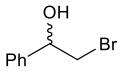
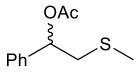
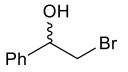
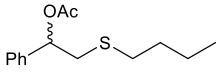
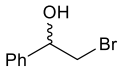
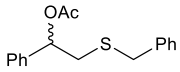
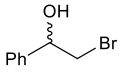
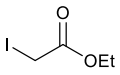
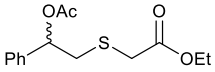
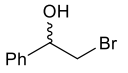
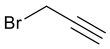
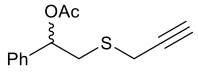
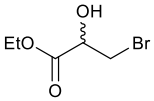
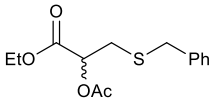
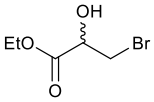
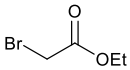
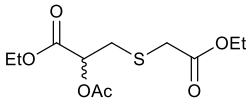
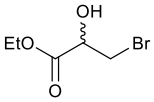
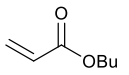
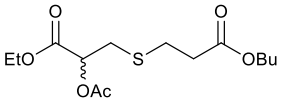
Table 3 One-pot synthesis of ß-acyloxy thioethers using alkyl- and aryl halohydrins and different electrophiles.[a]

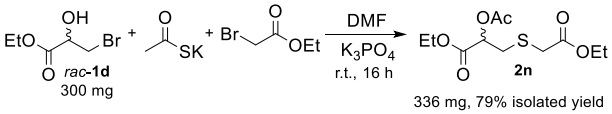


Entry	1	Electrophile	Base	Product	Yield (%)b
1		1a 	K_3PO_4	 2g	68
2		1b MeI	t-BuOK	 2h	68
3		1b $CH_3(CH_2)_3Br$	t-BuOK	 2i	53
4		1b 	K_3PO_4	 2j	85
5		1b 	t-BuOK	 2k	52
6		1b 	t-BuOK	 2l	61
7		1d 	t-BuOK	 2m	54
8		1d 	K_3PO_4	 2n	68
9		1d 	K_3PO_4	 2o	54

[a] For reaction conditions, see SI. [b] Isolated yields

For halohydrins **1a**, **1b**, and **1d**, alkyl, allyl, propargyl, benzyl and ester containing electrophiles were used, rendering the MCR products in good isolated yields (52-85%, Table 3, entries 1-8). Additionally, *n*-butyl acrylate was examined as electrophile employing ethyl 3-bromolactate **1d**, affording the corresponding thia-Michael adduct in 54% isolated yield (Table 3, entry 9).

Once the MCR reaction was optimized and the scope was explored, a higher scale multicomponent preparation of a ß-acyloxy thioether was tested. As shown in Scheme 4, 300 mg of rac-**1d** along with 1.1 equiv. of potassium thioacetate, 1.2 equiv. of ethyl bromoacetate and 1.2 equiv. of potassium phosphate in 2.5 mL of DMF furnished **2n** in 79% isolated yield. This compound is a suitable precursor of sulfur analogs of important phospholipids,[36] in particular sphingomyelin.[37]

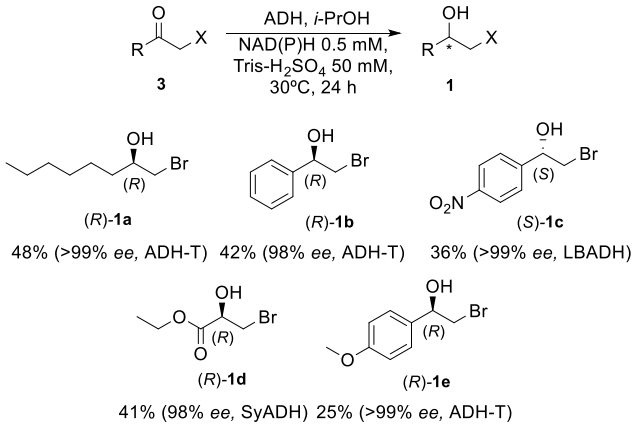


Scheme 4 Preparation of racemic **2n** at higher scale.

Having a robust MCR protocol for the direct synthesis of ß-acyloxy thioethers in our hands, we evaluated the stereochemical control of the products by feeding the system with enantioenriched halohydrins. Thus, based on our previous experience,[31,32,38] a biocatalytic approach was chosen for the preparation of the enantioenriched alcohols, an alternative that has been widely studied due to the importance of these compounds in pharmaceutical and chemical industry.[39]

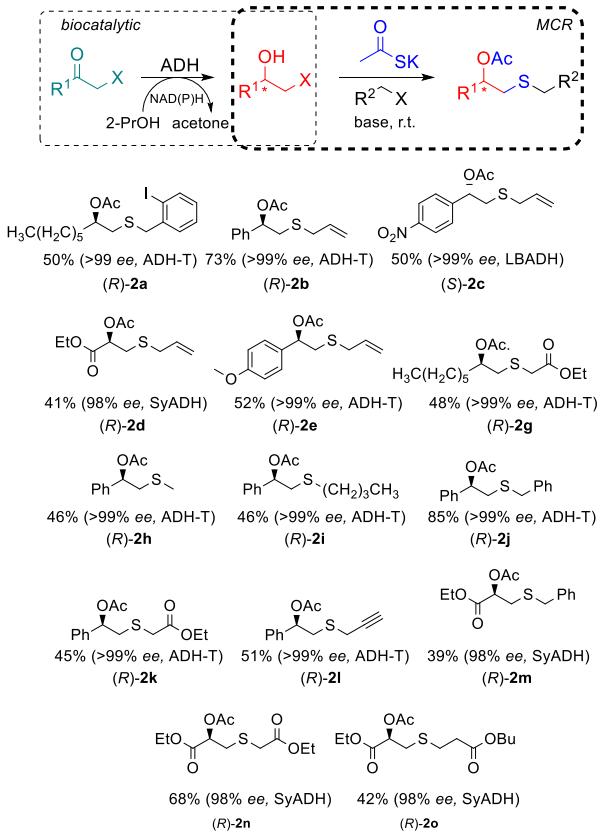
Considering the mentioned background, six different enzymatic preparations containing (*R*)- and (*S*)-selective alcohol dehydrogenases (ADHs) were employed for the stereoselective reduction of α-haloketones **3** at the expense of 2-PrOH (Table 4). These biocatalysts consisted of lyophilized whole cells of *E. coli* harboring an overexpressed recombinant protein (*E. coli*/ADH). The heterologously overexpressed enzymes in *E. coli* were ADH-A from *Rhodococcus ruber*, ADH-T from *Thermoanaerobacter* sp., TesADH from *Thermoanaerobacter ethanolicus*, SyADH from *Sphingobium yanoikuyae*, and LBADH from *Lactobacillus brevis*.[40]

With a suitable biocatalyst for the asymmetric preparation for each halohydrin (for biocatalysts screening, see Table S1, SI), the corresponding non-racemic compounds were synthesized. Using ADH-T, LBADH and SyADH-based enzymatic preparations, a catalytic amount of NAD(P)H, and 2-PrOH as hydrogen donor, the starting α-haloketones (**3**, 20 mM) were subjected to bioreduction at a semipreparative scale (0.44 mmol), affording moderate isolated yields and excellent *ee* for each desired halohydrin **1** (see Scheme 5).



Scheme 5 Synthesis of enantioenriched halohydrins employing ADHs.

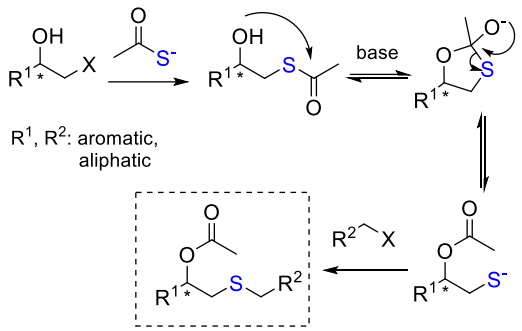
Then, MCRs were performed employing the enantioenriched halohydrins in order to synthesize the corresponding MCR products with defined stereochemistry (Scheme 6).



Scheme 6 Enantioenriched β-acyloxy thioethers synthesized through MCR employing enzymatically obtained enantioenriched halohydrins.

The enantiomeric excess of the resulting MCR products were compared to those of the corresponding starting halohydrins (see SI). As expected, no erosion of *ee* was observed, demonstrating that the *ee* of the substrate remained untouched during the course of the reaction. Hence, the mild basic medium was compatible with different functional groups and did not affect the stereochemical outcome of the reaction.

Regarding the multicomponent reaction mechanism, several [S→O] and [S→N] acyl migration examples employing transition metals such as Cu[41] and Pd,[42] or metal-free strategies,[43] have been reported. Based on a previously reported mechanism,[34] we proposed as a first step a S_N2 between the halohydrin and thioacetate anion, thus affording the corresponding ß-hydroxy thioacetate. Then, a base-promoted [S→O] acyl migration delivers the corresponding ß-acyloxy thiolate anion, which can be trapped with a suitable electrophile (alkyl halide or Michael acceptor, Scheme 7).



Scheme 7 Proposed mechanism for the Multicomponent Reaction.

Conclusions

In conclusion, a novel thiol-free MCR for the preparation of chiral ß-acyloxy thioethers has been successfully developed. The chemoenzymatic strategy relies on the high stereoselectivity of biocatalysis and the great bond forming power and versatility of MCRs. Hence, different aryl substitution patterns and functional groups were tolerated around the ß-acyloxy sulfide moiety. The stereochemistry of the final product could be easily modulated by providing the system with the proper (*R*)- or (*S*)-halohydrin, in this case obtained by stereoselective enzymatic reduction of the corresponding α-haloketone. Remarkably, the enantiopurity remained uneroded from the halohydrin to the final product, enabling the asymmetric synthesis of these fourteen ß-acyloxy thioethers for the first time, to the best of our knowledge. Interestingly, since no thiols are involved and air atmosphere is suitable, a simple reaction set up could be used, thus circumventing thiol-related common issues in organosulfur chemistry. Scaling up the MCR successfully rendered the desired compounds in high isolated yield. In fact, by working at higher scales, up to 96% isolated yields can be achieved. This methodology may provide straightforward access to valuable enantiopure and bioactive ß-acetoxy thioethers, sulfoxides and sulfones derivatives.[44]

Author Contributions

Conceptualization: F.R.B.; supervision: F.R.B., J.L.B, I.L.; investigation and formal analysis: M.G.L-V.; resources: F.R.B, J.L.B., I.L.; writing – original draft: M.G.L-V, F.R.B; writing – review and editing: all authors.

Conflicts of interest

There are no conflicts to declare.

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