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Organocatalytic conversion of arylglyoxals into optically active mandelic acid derivatives

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ABSTRACT

A novel protocol for the organocatalytic conversion of arylglyoxals into the corresponding α-hydroxy arylacetic acid methyl esters has been developed. The catalyst consists of a combination of a commercially available cinchona alkaloid derivative and an achiral thiol and leads to enantiomerically enriched products (ee_{max} 83%) under mild reaction conditions. The alkaloid can be easily recovered and reused without loss in activity and selectivity.

The synthesis of α-hydroxy arylacetic acids by means of intramolecular Cannizzaro reactions of the corresponding α-keto aldehydes is a process, which is known since the end of the 19th century.[1] The resulting mandelic acid derivatives are chiral molecules, which in the last decades proved to be versatile building blocks in the preparation of natural and biologically active compounds.[2] Stereoselective versions of intramolecular Cannizzaro reactions are rare since the conversion of the glyoxals commonly requires drastic reaction conditions such as strong bases in stoichiometric amounts and high temperatures, which limits the possibilities to render the process asymmetric. The use of Lewis acids allows for milder reaction conditions.[3] In combination with chiral ligands, enantioselective Lewis acid catalysts are formed, and up to now three systems have been reported.[4] Nishinaga found that cobalt(II) Schiff-base complexes (20 mol %) catalyzed the conversion of phenylglyoxal in a dichloroethane/isopropanol mixture at 60 °C, leading to 97% of isopropyl mandelate within 8 h. With a chiral Co-complex bearing a binaphthyl backbone, the product had 13.5% enantiomeric excess (ee).[4a] In 2000, Morken described the use of a Cu(II)/PhBox system as catalyst. In the presence of 1 mol % of a 1:1 complex of $Cu(OTf)_2$ and the phenyl-substituted bisoxazoline, phenylglyoxal hydrate was converted at room temperature to give mandelic acid isopropylester with 28% ee in 56% yield.[4b] Recently, this system was optimized by Ishihara, who employed 11 mol % of a bisoxazoline and 10 mol % of $Cu(SbF_6)_2$ in combination with *tert*-butanol instead of isopropanol. Under anhydrous conditions, the corresponding *tert*-butyl mandelate with 54% ee was obtained in 71% yield.[4c] With enantiopure menthol as nucleophile, diastereomeric interactions led to mandelic acid menthyl ester having up to 90% de.

Already from the 1950s stems another approach for the conversion of phenylglyoxal to mandelic acid esters. It was developed by Franzen,[5] who investigated the mechanism of the glyoxalase pathway.[6] This enzyme carries out the detoxification of methylglyoxal, which is produced in the metabolism of living organisms, by converting it into lactic acid. It consists of two enzymes (glyoxalase I and II) and catalytic amounts of the important coenzyme glutathione, a tripeptidic thiol. In the first step, a hemithioacetal is formed from the glyoxal and glutathione, which then isomerizes enantioselectively to the thioester by a base-mediated proton transfer catalyzed by glyoxalase I. Subsequently, glyoxalase II converts this thioester into the acid and glutathione.[7] Franzen utilized this concept in the conversion of phenylglyoxal to mandelic acid or the corresponding mandelates employing substoichiometric amounts of aminothiols as mediators.

The highest reaction rates were observed when *N*,*N*-dialkylcysteines were employed in methanol.[5b] Application of 20 mol % of a chiral aminothiol stemming from the reaction of thiiran with enantiopure *N*-methyl methamphetamin delivered methyl mandelate with 9% ee.[8] Franzen proposed the classical Cannizzaro mechanism involving a 1,2-hydride shift.[5a] Later, this was disproved by means of solvent isotope incorporation NMR experiments,[9] and it was shown that the rearrangement of hemithioacetal **2** to the α-hydroxy thiocarboxylic ester **4** proceeded by a general base-catalyzed enediol proton transfer (Scheme 1).[10] Subsequently, the intermediacy of enediol **3** was confirmed by flavin-trapping experiments.[11] Our ongoing research in the field of asymmetric organocatalysis[12,13] encouraged us to search for an improved enantioselective version of Franzen's Cannizzaro-type reaction. Herein, we describe the development of a metal-free procedure for the synthesis of mandelic acid derivatives **5** with easily accessible mediators leading to products with up to 83% ee.

The conversion of phenylglyoxal hydrate (**6a**) to methyl mandelate (**5a**) was selected as test reaction (Scheme 2). Based on Franzen's results, we initially varied the aminothiol structure, but to our disappointment all attempts to apply **7a–c** as chiral mediators[14]

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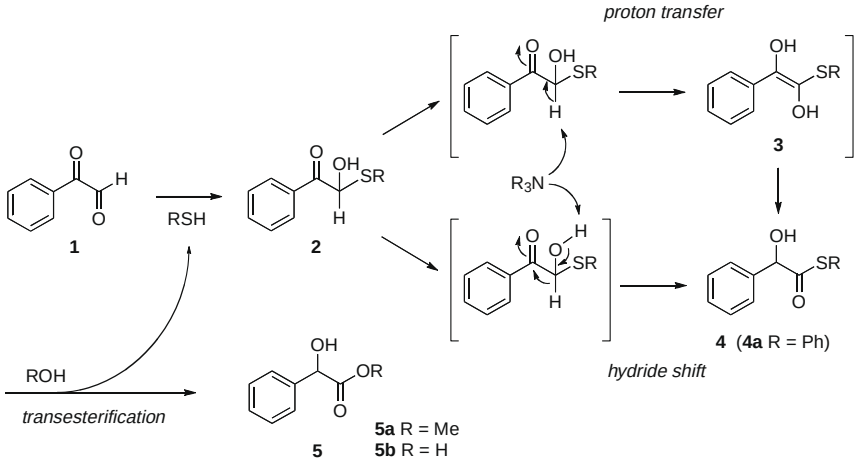
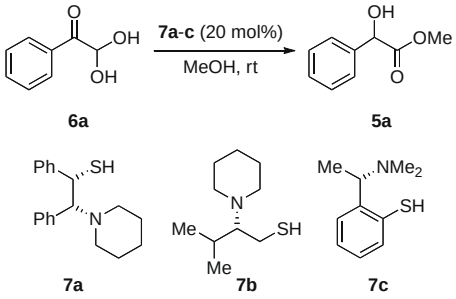


Scheme 1. Proposed mechanisms for the rearrangement of hemithioacetal **2** to thioester **4**.



Scheme 2. Conversion of phenylglyoxal hydrate (**6a**) in the presence of enantiopure aminothiols **7a–c**.

(in methanol) led to low product yields (up to 40%) and unsatisfying enantioselectivities (ee_{max} 12%). Since the access to enantiopure aminothiols is preparatively demanding, it appeared desirable to separate both functionalities, the amino and the thiol group. In preliminary experiments employing DABCO as amine and methanol as reaction media, aliphatic thiols gave only marginal yields of **5a**. In contrast, the use of thiophenols led to reasonable conversions in acceptable reaction times. Noting that the quinuclidine moiety of cinchona alkaloids contained a tertiary amino group and that various compounds of this substrate class have very successfully been applied in organocatalysis[15] (also in combination with thiols),[16] quinidine (**8a**) and its easily accessible derivatives (Fig. 1) appeared attractive for further tests.

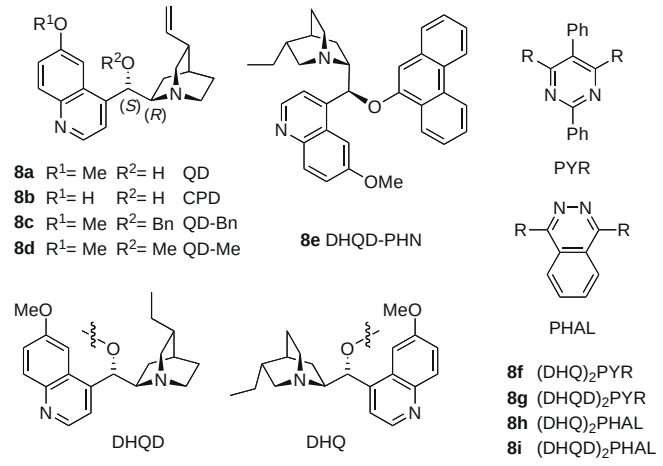
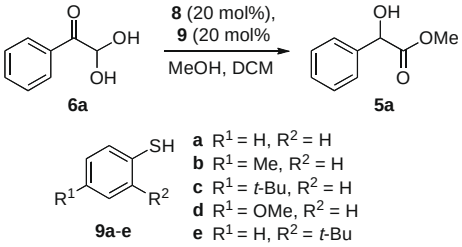


Figure 1. Cinchona alkaloid catalysts.

In order to prevent oligomerization, phenylglyoxal hydrate (**6a**) was first converted into its hemiacetal by stirring in methanol (1 mmol of **6a** in 2 mL of solvent). Subsequently, the alkaloid and the thiol (20 mol % each) were added. In the initial experiments, the presence of dichloromethane (DCM, 0.6 mL) ensured the complete dissolution of quinidine. Under standard reaction conditions, the resulting mixture was stirred at room temperature for 72 h. The results are summarized in Table 1.

Table 1
Catalyst screening in the enantioselective conversion of phenylglyoxal hydrate (**6a**) with chiral amines and achiral aromatic thiols[a].



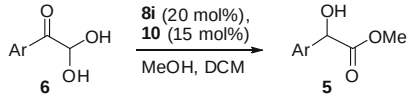
Entry	Alkaloid	Thiol	Yield[b] (%)	ee[c] (%)
1	QD (**8a**)	**9a**	60	9 (*R*)
2	QD (**8a**)	**9b**	58	9 (*R*)
3	QD (**8a**)	**9c**	59	9 (*R*)
4	QD (**8a**)	**9d**	57	11 (*R*)
5	QD (**8a**)	**9e**	40	13 (*R*)
6	CPD (**8b**)	**9a**	60	7 (*R*)
7	QD-Bn (**8c**)	**9a**	37	34 (*S*)
8	QD-Me (**8d**)	**9a**	43	50 (*S*)
9	DHQD-PHN (**8e**)	**9a**	41	55 (*S*)
10	$(DHQ)_2PYR$ (**8f**)	**9a**	48	55 (*R*)
11	$(DHQD)_2PYR$ (**8g**)	**9a**	53	53 (*S*)
12	$(DHQ)_2PHAL$ (**8h**)	**9a**	39	63 (*R*)
13	$(DHQD)_2PHAL$ (**8i**)	**9a**	41	69 (*S*)
14[d]	$(DHQD)_2PHAL$ (**8i**)	**9a**	49	56 (*S*)
15[e]	$(DHQD)_2PHAL$ (**8i**)	**9a**	58	58 (*S*)
16	$(DHQD)_2PHAL$ (**8i**)	**9e**	35	83 (*S*)

[a] Unless otherwise noted, the reactions were carried out with phenylglyoxal hydrate (**6a,** 1 mmol) and 20 mol % of both chiral amine and thiol in a mixture of MeOH (2 mL; 50 equiv) and DCM (0.6 mL) for 72 h at rt.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD-H column (90:10 heptane:isopropanol, 0.85 mL/min, 20 °C, 230 nm, $t_R(S)$ = 9.3 min, $t_R(R)$ = 15.6 min).
[d] Reaction was performed without DCM.
[e] Reaction was run 168 h.

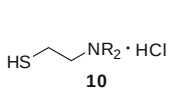
Application of a mixture of quinidine (**8a**) and thiophenol (**9a**) afforded methyl mandelate (**5a**) in 60% yield after 72 h (Table 1, entry 1).[17] Although the ee of the product was very low (9%), the experiment showed that the alkaloid was involved in the asymmetric protonation step and was capable to form an enantiomerically enriched product. Since in the studies of Ishihara the exclusion of water gave higher yields,[4c] anhydrous reaction conditions were tested next. Here, however, performing the reaction under argon in the presence of molecular sieves did not result in an improvement. The formation of significant amounts of mandelic acid (**5b**) by hydrolysis of the thioester was excluded by NMR spectroscopy. Small quantities of **5b** were only detected when water (2 equiv) was added. By reducing the catalyst loading or diluting the reaction mixture with other solvents such as DCM or toluene, slightly higher enantioselectivities were observed, and the reaction rate decreased significantly. Next, a set of thiophenol derivatives was tested under the standard reaction conditions (Table 1, entries 2–5). Even under argon, 2-thionaphthol and 4-nitrothiophenol were oxidized rapidly to the corresponding disulfides, resulting in termination of the catalysis at the initial stage. Electron-donating substituents in the *para*-position of the thiophenol had no influence on activity and selectivity (Table 1, entries 2–4). Only *ortho*-substituted 2-*tert*-butylthiophenol (**9e**) led to **5a** with a slightly higher ee (entry 5). In several other organocatalytic transformations, for example, Baylis–Hillman and Henry reactions, cinchona alkaloids with a phenolic hydroxy group in the C6′-position of the quinoline backbone showed superior selectivities in comparison to their natural analogs.[18] In contrast, nearly identical results were observed in the present system (entry 6).[19] A considerable improvement of enantioselectivity could be achieved with simple quinidine ethers, but it was accompanied by decreased yields (entries 7–9). Next, the effects of other cinchona alkaloid ethers, which nowadays are known as *Sharpless' ligands*,[20] were studied in the model reaction (entries 10–16). By employing $(DHQD)_2PHAL$ (**8i**) under standard conditions, methyl mandelate with up to 69% ee was isolated (entry 13). In contrast to quinidine (**8a**), the bisalkaloid ether was completely soluble in methanol. Attempts to perform the reaction without the co-solvent DCM led to a slightly decreased enantioselectivity (entry 14). Interestingly, the bisalkaloid ether of dihydroquinidine afforded methyl mandelate **5a** with opposite absolute configuration in comparison to the product obtained with the natural alkaloid (Table 1, entry 1 vs entry 13), a phenomenon that was also observed in other organocatalytic reactions.[20] Either enantiomer of methyl mandelate could be prepared by using quinine- or quinidine-derived catalysts (entries 10–13). By combining bisalkaloid **8i** with *ortho*-substituted thiophenol **9e**, the enantiomeric excess of the methyl mandelate could be further improved to 83% (entry 16). *To the best of our knowledge, this result represents currently the highest enantioselectivity achieved for the non-enzymatic conversion of phenylglyoxal to a mandelic acid derivative*. The yield was increased by prolonging the reaction time, but then the ee of the product was lower (entry 13 vs entry 15). Control experiments with enantiopure methyl mandelate excluded a racemization under the standard reaction conditions. On the other hand, highly enantiomerically enriched thiophenolester **4a**,[21] which was the initially formed product of the catalytic reaction (Scheme 1), showed a considerably lower enantiomeric excess after treatment with quinidine. Thus, the presence of this intermediate, which was detected in the model reaction as a by-product in significant amounts, and its slow (rate determining) transesterification with methanol to give the final product (**5a**) appeared responsible for the decrease of the ee with time (by rapid racemization). It also accounted for the low rate of the overall reaction, since significant amounts of the catalytically important thiol were trapped in an inactive form.

As mentioned earlier, Franzen had observed high reaction rates by using achiral dialkylcysteamines as catalysts.[5a,22] Assuming that the transesterification step in this system was accelerated by an anchimeric assistance of the amine function, we wondered whether the addition of an achiral β-aminothiol would increase the rate of the alkaloid catalysis. For evaluating this hypothesis, a combination of 15 mol % of 2-(*N*,*N*-dimethylamino)ethanthiol and 20 mol % of $(DHQD)_2PHAL$ (**8i**) was applied under standard conditions, and to our delight, after only 24 h methyl mandelate was obtained in 47% yield (Table 2, entry 1). Although the enantiomeric excess (57%) was slightly lower in comparison to the corresponding thiophenol experiment (Table 1, entry 13), the result was remarkable. It showed that even in the presence of considerable amounts of an achiral catalyst the alkaloid was the more active species in the thioester formation. Use of the commercially available hydrochloric salt **10a**, which is more stable toward oxidation and easier to handle, led to a slight increase in yield and ee (Table 2, entry 2). Prolonging the reaction time to 72 h had no significant beneficial effect on the yield, indicating that the conversion had nearly reached its maximum after 24 h (entry 3). Analogous results were observed by applications of the hydrochloric salts of 2-(*N*,*N*-diethylamino)ethanthiol (**10b**) and 2-(piperidino)ethanthiol (**10c**) (Table 2, entries 4 and 5).[23] In accordance with the observations of Franzen, use of the morpholino derivative **10d** led to a lower yield.[5b] Interestingly, this was accompanied by an increase in enantioselectivity (entry 6). Although the Sharpless' ligands are commercially available, it is important to note that $(DHQD)_2PHAL$ could be recovered and reused without loss of neither activity nor selectivity (entry 7). Reducing the catalyst loading at constant solvent volume resulted in a lower yield of **5a**. In contrast, by

Table 2
Catalyst screening of the enantioselective conversion of arylglyoxal hydrates **6** with alkaloid **8i** and achiral aminothiols.[a]



a Ar = Phenyl; **b** Ar = 2-Naphthyl; **c** Ar = 1-Naphthyl



10a R = -Me
10b R = -Et
10c R = $-C_4H_8-$
10d R = $-C_2H_4OC_2H_4-$

Entry	Substrate	Aminothiol	Yield[b] (%)	ee[c] (%)
1[d]	**6a**	**10a**	47	57 (*S*)
2	**6a**	**10a**	52	63 (*S*)
3[e]	**6a**	**10a**	55	59 (*S*)
4	**6a**	**10b**	48	59 (*S*)
5	**6a**	**10c**	46	59 (*S*)
6	**6a**	**10d**	27	72 (*S*)
7[f]	**6a**	**10b**	46	61 (*S*)
8[g]	**6a**	**10b**	42	63 (*S*)
9	**6b**	**10b**	44	56 (*S*)[h]
10	**6c**	**10b**	66	65 (*S*) [i]

[a] Unless otherwise noted the reactions were carried out with arylglyoxal hydrate (1 mmol), $(DHQD)_2PHAL$ (20 mol %), and aminothiol hydrochloride (15 mol %) in MeOH (2 mL; 50 equiv) for 24 h at rt.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD-H column (90:10 heptane/isopropanol, 0.85 mL/min, 20 °C, 230 nm, $t_R(S) = 9.3$ min, $t_R(R) = 15.6$ min).
[d] The aminothiol was used as free base.
[e] Reaction run for 72 h.
[f] Reaction run with recycled catalyst.
[g] Use of 10 mol % of $(DHQD)_2PHAL$ and 7.5 mol % of **10b** in 1 mL of MeOH.
[h] Determined by HPLC analysis using a Chiralcel OD–H column (90:10 heptane:isopropanol, 1 mL/min, 20 °C, 230 nm, $t_R(S) = 11.8$ min, $t_R(R) = 14.1$ min).
[i] Determined by HPLC analysis using a Chiralcel AD-H column (90:10 heptane:isopropanol, 0.8 mL/min, 20 °C, 230 nm, $t_R(S) = 20.1$ min, $t_R(R) = 22.1$ min).

halving both the amount of solvent and the catalyst quantity no significant change of yield and enantioselectivity was observed (Table 2, entry 8). To extend the substrate scope, 1-naphthylglyoxal hydrate (**6b**) and 2-naphthylglyoxal hydrate (**6c**) were prepared by Riley oxidation of the corresponding methyl ketone. Subjected to the alkaloid catalysis with $(DHQD)_2PHAL$ and hydrochloride **10b**, the corresponding α-hydroxy arylacetic acid methylesters were formed with 56% ee and 65% ee, respectively (Table 2, entries 9 and 10).

In summary, we have developed a novel organocatalytic protocol for the conversion of arylglyoxals to the corresponding α-hydroxy arylacetic acid methyl esters. Readily available cinchona alkaloid catalysts in combination with achiral thiols deliver enantiomerically enriched products with good ees. The reaction rate could be accelerated by presence of achiral β-aminothiols as the thiol component.

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