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Direct Synthesis of β-Hydroxy-α-amino Acids *via* Diastereoselective Decarboxylative Aldol Reaction

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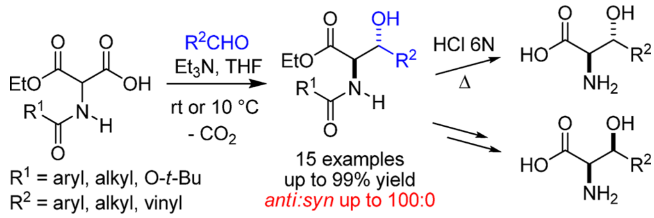
ABSTRACT



A straightforward metal-free synthesis of *anti*-β-hydroxy-α-amino acids is described. The organic base-mediated decarboxylative aldol reaction of cheap, readily available α-amidohemimalonates with various aldehydes afforded under very mild conditions *anti*-β-hydroxy-α-amido esters in high yields and complete diastereoselectivity. Simple one-pot subsequent transformations enabled the corresponding *anti*-β-hydroxy-α-amino acids or in a few examples their *syn* diastereomers to be obtained directly using epimerization conditions.

β-Hydroxy-α-amino acids are important biomolecules and building blocks for the synthesis of many biologically active compounds such as ristocetin or teicoplanin[1] of the vancomycin family and many other biological substances.[2] In recent years, numerous strategies have been reported for the synthesis of β-hydroxy-α-amino acids, the main challenge focusing on the control of the relative and absolute stereochemistry of the asymmetric carbons. The Sharpless aminohydroxylation reaction is an efficient method to append stereoselectively these two groups in one step.[3] Dihydroxylation is also an efficient pathway, although it requires additional steps.[4] The stereoselective reduction of a ketone by transition-metal-catalyzed hydrogenation using readily available α-amido-β-ketoesters has been explored to synthesize the target compounds.[5]

A powerful strategy aims to create directly the covalent bond between the two vicinal groups, the amine and alcohol. For the synthesis of β-hydroxy-α-aminoacid derivatives, a classic route involves aldol reactions of Schöllkopf's glycine enolate with aldehydes,[6] and more recently using glycine Schiff bases[7] or α-isocyano acetates[8] as donors. In the current trend of sustainable development,

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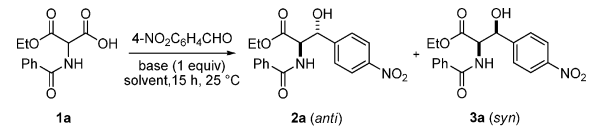
organic chemists intend to find simple and mild conditions, using naturally occurring molecules. In connection with these objectives, we report thereafter the decarboxylative aldol reaction of functionalized α-amino-Malonic Acid Half Oxyesters (MAHOs) as cheap glycine equivalents with aldehydes under very mild metal-free conditions for the direct synthesis of polyfunctional esters.

Malonic acid and its derivatives have been used in various reactions as acetic acid equivalents due to the ease of functionalizing the central methylene and then to decarboxylate. MAHOs and MAHTs (Malonic Acid Half Thioesters), having a free carboxylic acid group, add directly under mild conditions onto various electrophiles with concomitant loss of CO_2. Of particular interest are the decarboxylative Claisen,[9] Aldol or Mannich,[10] Michael,[11] and the Knoevenagel–Doebner[12] reactions with those substrates. In most reports, the starting hemimalonates are unsubstituted on the central methylene because of the lower reactivity of similar substrates bearing an alkyl group.[10b,d−f] The amido-MAHOs, easily obtained from the cheap amidomalonate diesters, have been rarely used in those reactions,[13] although they afford potentially highly functionalized products.

We became interested in those amido-MAHO derivatives while studying their asymmetric decarboxylative protonation for a direct access to enantioenriched α-amino acids.[14] Following our initial work on the decarboxylative Aldol (and Mannich) reaction with unsubstituted MAHOs,[10f] we envisaged this reaction sequence with amido-MAHOs where two consecutive stereogenic centers are established in a single operation. We focused on developing mild metal-free conditions and on the control of the *syn*/*anti* diastereoselectivity.

Table 1. Decarboxylative Aldol Reaction of **1a**[a]



entry	solvent	base	dr[b] (*anti*/*syn*)	yield (%)
1	DMF	Et_3N	93/7	71%
2	DMF	Et_3N	100/0	63%[c]
3	DMF	DIPEA	77/23	79%
4	THF	DIPEA	88/12	92%
5	EtOH	Et_3N	94/6	83%
6	DCM	Et_3N	100/0	70%
7	CCl_4	Et_3N	96/4	93%
8	THF	Et_3N	100/0	92%
9	THF	Et_3N	100/0	92%[d]
10	THF	Et_3N	100/0	74%[e]
11	THF	DMAP	100/0	99%
12	THF	DABCO	100/0	99%
13	EtOH	KOH	1/1	80%
14	THF	–	1/1	70%[f]

[a] Conditions: **1a** (0.4 mmol) with 4-nitrobenzaldehyde (0.48 mmol, 1.2 equiv) and the base (0.4 mmol, 1 equiv) in 0.7 mL of solvent, 15 h at rt. [b] Diasteromeric ratios were determined by ^1H NMR analysis of the crude. [c] At 10 °C. [d] Using 7 mol % of Et_3N. [e] Carried out on 1 g of **1a** (4 mmol) using 5 mol % of Et_3N. [f] 48 h at rt.

The reaction of benzamido-MAHO **1a** with 4-nitrobenzaldehyde was first studied in various solvents at rt (Table 1).

To optimize the decarboxylative aldol reaction, selected bases were screened in various solvents at rt. In a first attempt in DMF, triethylamine showed a promising result affording the aldol products in 71% yield and a 97/3 diastereomeric ratio in favor of the *anti*-adduct **2a** (entry 1). Decreasing the temperature slightly to 10 °C enabled **2a** to be obtained with complete *anti* selectivity (entry 2). With the bulkier base DIPEA, the diastereomeric ratio dropped to 77/23 in DMF (entry 3) and 88/12 in THF (entry 4). Several solvents were tested with Et_3N (entries 5–8). In THF and DCM the reaction gave only the *anti*-diastereomer **2a** in 92% and 70% yield, respectively. The reaction performed using a substoichiometric amount of Et_3N (7 mol %) led to the same result, high yield and selectivity (entry 9). On a gram scale of **1a**, with only 5 mol % of Et_3N, the reaction yielded **2a** as the sole diastereomer in good yield (entry10). Other bases such as DMAP and DABCO led to the same high levels of selectivity and yield in THF (entries 11–12). Potassium hydroxide afforded the aldol products in good yields but without selectivity (entry 13). The reaction without a base gave the product yet in a longer reaction time and with a 1/1 diastereomeric ratio (entry 14). This illustrates the catalytic effect of amine bases and their beneficial effect on the selectivity. To confirm that no epimerization of the product occurred once it is formed, treatment of **2a** as an *anti*/*syn* diastereomeric mixture (2/1 ratio) with Et_3N in THF afforded the same ratio after 4 days at rt. As the cheapest of the most

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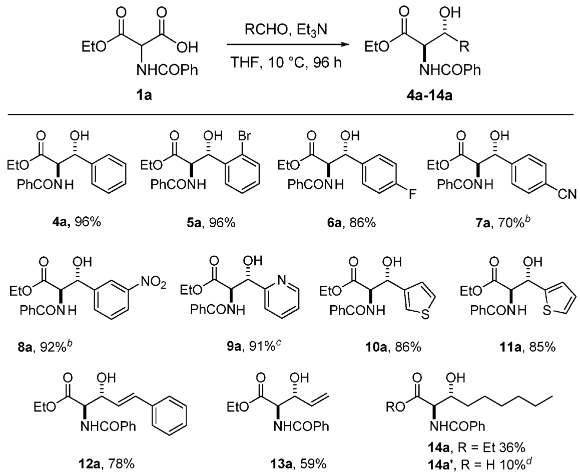
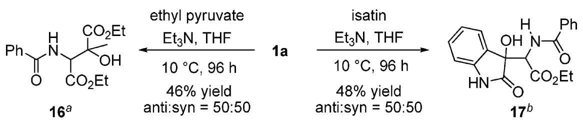
Scheme 1. Scope of the Decarboxylative Aldol Reaction[a]



[a] Conditions: **1a** (0.4 mmol), RCHO (1.6 mmol, 4 equiv), Et_3N (0.4 mmol) in 0.2 mL of THF. [b] RCHO (0.48 mmol, 1.2 equiv), rt, overnight. [c] 24 h. [d] Acid **14a′** is produced after work up, see Supporting Information (SI) for details.

Scheme 2. Decarboxylative Aldol Reaction with Activated Ketones



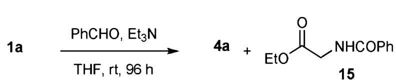
[a] **16** (*anti* and *syn*) were isolated with **15** in a 4/1 ratio, see SI. [b] Isolated diastereomers.

efficient bases tested, Et_3N was chosen for the following part of this work.

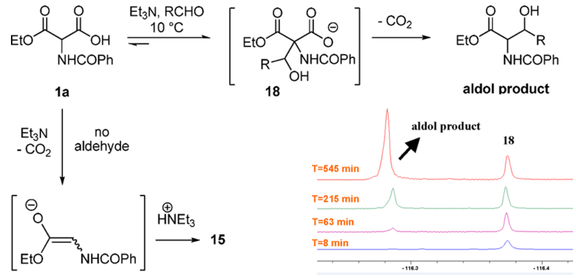
The scope of the reaction was then examined with various aldehydes to afford β-hydroxy-α-amido esters **4a**–**14a** (Scheme 1). In THF at rt and with the less reactive benzaldehyde,[10b,d,e] the reaction gave a mixture of *anti*-aldol **4a** and glycine derivative **15**.[15]

However, at lower temperature, the aldol product **4a** was obtained in 96% yield as the sole compound (Scheme 1). This result showed the higher reactivity of α-amido-MAHO compared to α-alkyl substituted MAHOs since the reaction with benzaldehyde provided the aldol product in excellent yield. These optimized conditions (4 equiv of aldehyde at 10 °C, 96 h) were applied to aromatic, heteroaromatic, vinylic, and aliphatic aldehydes. The *anti*-aldol adducts **5a**–**11a** were obtained in good yields from *ortho*-, *meta*-, and *para*-aryl or heteroaryl aldehydes. Importantly, α,β-unsaturated aldehydes such as acrolein and cinnamaldehyde underwent 1,2 addition to give the corresponding aldol adducts **12a** and **13a** in 78% and 59% yield respectively,

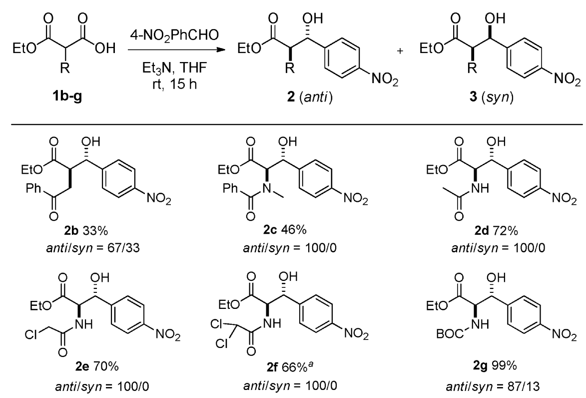
(15) The reaction afforded **4a** and **15** in 39% and 49% yield respectively.



Scheme 3. Mechanistic Pathways for the Decarboxylation of **1a**



Scheme 4. Substrate Scope of α-Substituted MAHOs



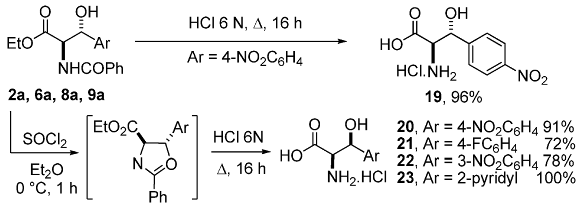
[a] Reaction carried out at 10 °C.

along with recovered starting material in the case of **13a**. Usually, such aldehydes cannot be used in organocatalyzed aldol reactions due to side reactions occurring with amine-based organocatalysts. With heptanal, the reaction was slower and provided a mixture of *anti*-products **14a** and **14a′** in 46% combined yields along with 38% of recovered starting MAHO **1a**. No aldol product was obtained in the reaction of **1a** with *para*-methoxybenzaldehyde or pivalaldehyde (not shown in Scheme 1). In both cases, only starting materials were recovered along with an equal molar amount of **15**. To further evaluate the scope of the reaction, isatin and pyruvate, which are well-known activated ketones for reaction with MAHTs,[10d,g] were used. They led to products **16** and **17** respectively in satisfactory yields but without any diastereoselectivity (Scheme 2).

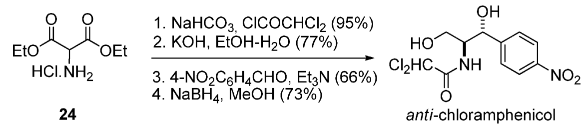
Based on previous studies[10b−e] including our own[10f] the formation of aldol products can occur via two mechanisms: MAHO undergoes first a decarboxylation generating an enolate which then adds onto the aldehyde, or reaction of MAHO with the aldehyde occurs before the CO_2 loss.

The reaction was monitored by ^{19}F NMR by using 4-fluorobenzaldehyde (peak at −103.86 ppm) and quickly showed a small peak at −116.36 ppm, assigned to intermediate **18** and later confirmed by ^{1}H and ^{13}C NMR. After a few minutes, this peak disappeared along with the occurrence of the *anti*-aldol peak at −116.25 ppm (Scheme 3). The presence

Scheme 5. Deprotection and Epimerization of the Aldol Products



Scheme 6. Synthesis of *anti*-Chloramphenicol



or the nature of the aldehyde was investigated to explain the formation of the protonated side-product **15**. The previous reaction of **1a** with benzaldehyde showed no side product at 10 °C whereas 49% of **15** was obtained at 25 °C. The decarboxylation of the same acid **1a** without benzaldehyde gave **15** in 34% yield after 15 h at rt and only 10% yield at 10 °C after 15 h. Overall, at rt the slow decarboxylation of **1a** produced exclusively glycine derivative **15** and probably not the aldol adduct. In the presence of an aldehyde, it occurred concurrently with the rapid aldol reaction of MAHO and subsequent decarboxylation of intermediate **18**. The side protonation is almost completely inhibited at 10 °C and is in most cases overwhelmed by the decarboxylative aldol reaction.

Several protected α-amino groups (MAHOs **1c**–**g**) were also tested in this sequence to evaluate their role in the reactivity and selectivity of the reaction (Scheme 4).

By comparison, the aldol reaction of MAHO without a nitrogen substituent (**1b**) was assessed under similar conditions. As expected, using alkyl-MAHO **1b**, a low reactivity was observed with a poor *anti*/*syn* ratio. MAHO **1c** having a tertiary amide substituent was prepared. It afforded only the *anti*-product **2c** albeit in moderate yield. These results confirm the influence of the nitrogen substituent of MAHO on the selectivity and may reflect the role of the N–H moiety on the reactivity. *N*-Acetyl **1d**, *N*-chloroacetyl **1e**, and *N*-dichloroacetyl **1f** led to good yields and *anti* diastereoselectivity. When we changed to bulkier *N*-Boc, the selectivity was slightly affected with an 87/13 *anti*/*syn* ratio but the yield was excellent. As observed previously (see Table 1, entries 1 and 2), the selectivity should be improved by carrying out the reaction at 10 °C.

From all these observations, it appears that the level of diastereoselectivity depends on not only the nature of the electrophile (aldehyde or ketone) but also the presence of an amide group as the substituent of the starting MAHO.[16]

Deprotection of the aldol adduct **2a** was achieved in aqueous HCl and afforded the *anti*-β-hydroxy-α-amino acid **19** in 96% yield without epimerization (Scheme 5).

Finally, a simple one-pot procedure was developed to synthesize selected *syn*-β-hydroxy-α-amino acids. The reaction of *anti*-aldol products **2a**, **6a**, **8a**, and **9a** with thionyl chloride gave an oxazoline intermediate subsequently hydrolyzed to yield the deprotected compounds **20**–**23** with complete inversion of the stereocenter bearing the alcohol (Scheme 5).

The synthesis of the antibiotic chloramphenicol[17] is an attractive application of this methodology. Xu et al.[18] have recently developed a rapid access in two steps to the natural *syn* diastereomer from amino acid **19**. The direct and efficient synthesis of the *anti*-chloramphenicol from commercial diethylaminomalonate **24** is described in Scheme 6.

Acylation of commercial aminomalonate **24** followed by saponification with 1 equiv of potassium hydroxide afforded the corresponding amido-MAHO **1f**. We then successfully applied the decarboxylative aldol reaction which after reduction of the aldol adduct **2f** with $NaBH_4$ gave *anti*-chloramphenicol in 35% overall yield. Thus, *anti*- and *syn*-chloramphenicol are quickly available under these mild conditions.

In summary, although decarboxylative reactions of simple MAHOs are known, we have unveiled the synthetic potential of α-amido-MAHOs in organocatalyzed decarboxylative aldol reactions using aminomalonate derivatives as cheap starting material. *anti*-β-Hydroxy-α-amino esters are obtained directly and exclusively in high yields from various aldehydes. Noteworthy are the results observed with α,β-unsaturated aldehydes which react for the first time with MAHOs. Preliminary mechanistic studies showed possible pathways undertaken by α-amido-MAHO under base catalysis. At low temperature, addition onto the aldehyde is favored over the concurrent decarboxylative protonation. Deprotection of aldol products led to the corresponding *anti*-β-hydroxy-α-amino acids and epimerization under selected conditions to their *syn* diastereomers. Overall this metal-free procedure provides a useful and direct access to highly functionalized esters with complete control of the relative stereochemistry from cheap starting material. This decarboxylative aldol reaction should find wide applications for the synthesis of natural products of interest in chemistry and biology. The enantioselective version of the reaction is currently under investigation and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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