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Enantioselective Synthesis of *anti*- β -Hydroxy- α -amino Esters via an Organocatalyzed Decarboxylative Aldol Reaction

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Abstract The first enantioselective decarboxylative aldol addition with α -amido substituted malonic acid half oxyesters (MAHOs) is described. The combined use of a newly designed bifunctional sulfonamide catalyst with pentafluorobenzoic acid as an additive afforded the β -hydroxy- α -amino acid derivatives in moderate to high yields and with high enantioselectivities.

Key words bifunctional organocatalyst, malonic acid half oxyester (MAHO), cinchona alkaloid, sulfonamide, β -hydroxy- α -amino acid

anti- β -Hydroxy- α -amino acids form key components of various natural products¹ and are highly versatile synthons for molecular synthesis. Stereoselective methods for their synthesis include asymmetric ruthenium-catalysed hydrogenation via dynamic kinetic resolution² (DKR), rhodium-catalysed multicomponent reactions,³ and aldol additions mediated by metals⁴ or organocatalysts.⁵ Recently Rouden reported a metal-free decarboxylative aldol addition with α -amino substituted malonic acid half oxyesters (MAHOs).⁶ In the presence of an achiral tertiary amine base, the highly reactive α -amido MAHOs underwent diastereoselective addition to various aldehydes, generating racemic products with $\geq 100:1$ *anti/syn* selectivity. Inspired by this result, we sought to develop an enantioselective version as a continuation of our research into bifunctional organocatalysis, and herein present an overview of our research towards this goal.

The use of MAHOs and malonic acid half thioesters (MAHTs) as substrates exploits the ability of carboxylic acids to decompose via CO₂ expulsion, allowing reactive enolate intermediates to be generated under almost neutral conditions and with minimal waste. While MAHOs have found limited use⁷ due to the low acidity of the methylene protons, MAHTs, which have considerably lower pK_as, have proven good substrates in

several organocatalyzed decarboxylative aldol-type reactions.⁸ Yet, these reactions all rely on highly reactive electrophiles i.e., isatins and trifluoromethyl ketones, for good results, illustrating the relatively poor reactivity of such substrates. Significant advances were made by Song and List,^{8g} whose chiral sulfonamide catalyst mediated the decarboxylative addition of MAHTs to aldehydes in 73–94% ees and in yields of up to 96% for electron deficient aldehydes, although reactions required a catalyst loading of 30% and up to 96 hours for completion. However, these examples all deal with unsubstituted MAHTs and thus are limited to the creation of one new stereocenter; simultaneously generating *two* new stereocenters under high stereocontrol presents a huge additional challenge.⁹

Despite the great potential of α -amido MAHOs for organic synthesis, their use in decarboxylative reactions is rare, likely hindered by difficulties associated with their synthesis and stability. To date, no method for the preparation of α -amido MAHTs has been reported, and thus their reactivity in such reactions is unknown. Therefore, there is enormous room for innovation in this area regarding both the synthesis and applications of these malonic acids.

During our preliminary studies into the decarboxylative aldol addition with MAHOs, a 1:1 ratio of highly reactive *p*-nitrobenzaldehyde and *N*-Boc MAHO **1a** were employed as model substrates to screen a range of structurally diverse bifunctional organocatalysts, including ureas, thioureas, squaramides, benzothiadiazines, sulfonamides and boronic acids.¹⁰ After 48 hours in THF at room temperature, sulfonamide catalyst **3** (10 mol %) proved most effective, affording the β -hydroxy- α -amino ester **4a** in 45% yield and 66:34 er, with 88:12 *anti/syn* ratio (see entry 1, Table 1).

Using this catalyst in subsequent experiments to explore the MAHO structure (Table 1), Fmoc/Ph protected **1j** was identified as the preferred MAHO substrate (48% yield, 74:26

er, 80:20 dr; entry 10). Given the prevalence of Fmoc protection in solid-phase peptide synthesis (SPPS) and other synthetic applications, the ability to generate these pre-protected products in a single step was an ideal result. Interestingly, an *N*-acetyl group reversed the diastereoselectivity of the reaction (5:2 *syn/anti*; entry 2), while use of an *N*-tosyl protecting group rendered the reaction almost completely non-selective (55:45 er, 1:1 dr; entry 7), perhaps due to undesirable intra- or intermolecular hydrogen bonding. The choice of ester appeared to have less of an influence on reaction selectivity.

Table 1 Investigation of MAHO structure in the decarboxylative aldol reaction with *p*-nitrobenzaldehyde and sulfonamide catalyst **3**

Entry	MAHO (R ¹ , R ²)	Product	Yield (%) ^a	<i>anti</i> : <i>syn</i> ^b	er ^c
1	1a (Et, Boc)	4a	45	88:12	66:34
2	1b (Et, Ac)	4b	51	29:71	60:40
3	1c (Et, Bz)	4c	41	86:14	72:28
4	1d (Et, <i>o</i> -F-Bz)	4d	44	75:25	67:33
5	1e (Et, Cbz)	4e	19	80:20	70:30
6	1f (Et, Fmoc)	4f	37	75:25	76:24
7	1g (Et, Ts)	4g	21	50:50	55:45
8	1h (Me, Bz)	4h	33	94:6	65:35
9	1i (Ph, Bz)	4i	38	88:12	73:27
10	1j (Ph, Fmoc)	4j	48	80:20	74:26

^a Isolated yields of *syn* and *anti* isomers.

^b Determined by ¹H NMR analyses of crude reaction mixture.

^c Determined by chiral HPLC analyses.

This *N*-Fmoc/Oph combination presented a problem for large-scale synthesis of MAHO starting materials, however, with the Fmoc group suffering from substantial decomposition in the rhodium catalysed N-H insertion reaction previously used to synthesize our α -amido MAHOs. Furthermore, the base-labile phenyl ester is incompatible with conditions typically employed for Fmoc protection. In a new approach, we developed a novel direct protecting group exchange of a diphenylmethyl group for Fmoc under hydrogenolysis conditions (Scheme 1).

Scheme 1 Preparation of MAHO (**1j**) and MAHT (**10**)

By poisoning the Pd catalyst with 2,2'-bipyridyl, the Ph₂CH moiety was cleaved while leaving the Fmoc group—which can

be unstable under such conditions—intact. The same methodology was also applied to the synthesis of the corresponding MAHT (**10**), with the thioester moiety having no detrimental effect on the catalyst. Both substrates were ultimately prepared on a multigram scale in excellent overall yield,¹⁰ and storage below 0 °C ensured their stability for weeks or months. Both the synthesis of α -amido MAHTs and this protecting group exchange are previously unreported in the literature.

With adequate MAHO in hand, and having previously narrowed down the preferred catalyst type, a range of aryl sulfonamides bearing chiral amine substituents were screened in the decarboxylative aldol reaction between MAHO **1j** and *p*-NO₂PhCHO (**2**).¹⁰ Cinchona alkaloid derivatives were clearly superior to other chiral amines, while the presence of an *ortho*-substituent on the sulfonamide aryl ring proved essential for high enantio- and diastereoselectivity. Trimethoxyphenyl catalyst **11** ultimately gave the best results, affording the product (**13c**) in 70% yield, 90:10 er, and 72:18 *anti/syn* ratio. Despite extensive modelling, synthesis and screening of aryl sulfonamides with diverse *o*, *m*, and *p*-substituents, a direct relationship between selectivity and either steric size or electronic effects was not observed, which made further refinement of catalyst structure difficult.

Cinchona alkaloid conformations are known to be highly dependent on solvent and temperature,¹¹ and optimal orientation of the catalyst's quinoline and quinuclidine rings in the transition state is crucial for selective positioning of substrates via hydrogen bonding. Etheral solvents, which interact strongly with the catalyst and substrates, were found to give the best results; performing the model reaction in cyclopentyl methyl ether (CPME) at room temperature afforded the product in 84% yield, 89:11 er, and 81:19 dr. The absence of strong hydrogen bonding networks, as with chlorinated or hydrocarbon solvents, led to a reduction in selectivity and yields, with only 28% of product obtained in toluene.¹⁰

Protic additives had little effect on reaction stereoselectivity but produced a notable increase in yields. This catalytic effect was largely independent of additive acidity, sterics or electronic properties, with pentafluorobenzoic acid ultimately selected due to ease of use. ¹H NMR studies in THF-*d*₈ showed marked changes in catalyst shape following additive addition, but ultimately failed to elucidate the exact mechanistic role of the additive.

Both dr and er were improved by lowering the concentration from 0.1M to 0.05M; yields suffered considerably at 0.025M due to decarboxylation-protonation of the MAHO, which competes with the aldol reaction pathway to give the corresponding glycine derivative. Performing the addition at 15 °C helps to mitigate this unproductive side reaction, however yields with poorly reactive aldehydes still suffer as a result of by-product formation. Given the superior reactivity of MAHTs with these substrates, it was postulated that their reaction with poor electrophiles may be faster, giving higher yields. While reactions with **10** were significantly faster, the higher instability of α -amido MAHTs also led to a greater rate of by-product formation. Furthermore—and quite unexpectedly—stereocontrol was almost non-existent, even at

0 °C (52:48 er and 45:55 dr), a result that was repeated with other organocatalysts tested. Variations in solvent and temperature did not lead to improvements, and thus the application of MAHTs to this reaction was not further pursued.

In an effort to counter by-product formation and low yields, reaction stoichiometry was then adjusted in favour of excess aldehyde, which should increase the likelihood of aldol addition vs MAHO protonation. Using 5–10 equiv. of the inexpensive and readily available aldehydes improved yields substantially, particularly with less reactive substrates such as *o*-NO₂PhCHO, which went from 34% with 1.5 equiv. of MAHO to 76%. Gratifyingly, no reduction in enantio- or diastereoselectivities were observed—in fact, er and dr generally increased slightly.¹⁰

Exploring the scope of the reaction under these newly optimised conditions, a series of aldehydes were treated with MAHO **1j** in the presence of catalyst **11** and C₆F₅COOH (20 mol %). The results can be seen in Table 2. Aldehydes bearing electron withdrawing groups such as NO₂ (entries 1–3) and CN (entry 5) reacted rapidly, affording the β-hydroxy-α-amino esters in yields of between 90–99%. Of these, *o*-NO₂PhCHO was notably slower to react due to steric hindrance, but gave the highest er of all substrates (95:5, with 86:14 dr). *p*-Br and *o*-Cl benzaldehydes gave yields of only 68% (entry 4) and 60% (entry 8), respectively, reflecting their decreased electrophilicity, and in the case of the latter, steric hindrance. In all these examples, the er was typically ≥ 91:9, and the dr ≥ 83:17.

As expected, reactions with poor electrophiles suffered from competing glycine formation, with *m*-anisaldehyde and benzaldehyde giving yields of only 41% (entry 9) and 46% (entry 10), respectively, even after prolonged reaction times and at increased concentration. The enantioselectivity also fell, with er's of 87:13 in both cases. 2-Naphthaldehyde gave a similar result (entry 12; 49%, 89:11 er, 84:16 dr), while the highly deactivated *p*-anisaldehyde failed to give any product

after 2 days. The alkene cinnamaldehyde proved compatible with the amine organocatalyst, and despite giving the product in only 36% yield due to low reactivity, the er was an excellent 94:6 (entry 11, 81:19 dr). The decarboxylative aldol reaction was also applicable to heterocyclic aldehydes with varying results: 3-thiophenecarboxaldehyde was slow to react, and gave a poor 23% yield, with 84:16 er and 83:17 dr (entry 13), while reaction with 5-bromo-2-furaldehyde was complete after 20 h, affording the product in 62% yield, 85:15 er and 81:19 dr (entry 14). The diminished stereoselectivity of these two reactions is perhaps a result of undesirable coordination between the heteroatom of the aldehydes and the catalyst and/or MAHO.

Scheme 2 Determination of the absolute configuration

For determination of the absolute stereochemistry, β-hydroxy-α-amino ester **4j** was transesterified to the methyl ester under mild conditions¹² (Scheme 2). After separation of the *anti* isomer (73% ee), the Fmoc group was removed and the amine reprotected with BzCl to give benzoyl derivative **16**. Comparison of optical rotation data to known amino ester *ent*-**16**^{2c} established the configuration of our β-hydroxy-α-amino esters as (*S,S*).

Table 2 Scope of decarboxylative aldol reaction between **1j** and various aldehydes, mediated by sulfonamide catalyst **11**.

Entry	R	Equiv. RCHO	Conc (M)	Time (h)	Product	Yield (%) ^a	<i>anti:syn</i> ^b	er ^c
1	<i>o</i> -NO ₂ C ₆ H ₄	10	0.05	16	13a	90	86:14	95:5
2	<i>m</i> -NO ₂ C ₆ H ₄	10	0.05	16	13b	99	89:11	93:7
3	<i>p</i> -NO ₂ C ₆ H ₄	10	0.05	3	4j	95	88:12	89:11
4	<i>p</i> -BrC ₆ H ₄	10	0.05	18	13c	68	85:15	92:8
5	<i>p</i> -CNC ₆ H ₄	10	0.05	16	13d	95	89:11	93:7
6	<i>p</i> -CF ₃ C ₆ H ₄	10	0.05	16	13e	73	88:12	93:7 ^d
7	<i>p</i> -OMeC ₆ H ₄	10	0.05	48	13f	Trace	—	—
8	<i>o</i> -ClC ₆ H ₄	5	0.1	20	13g	60	90:10	91:9
9	<i>m</i> -MeOC ₆ H ₄	5	0.1	72	13h	41	83:17	87:13
10	C ₆ H ₅	10	0.1	65	13i	46	88:12	87:13
11	CH=CHPh	10	0.1	65	13j	36	81:19	94:6
12	2-Naphthyl	10	0.1	48	13k	49	84:16	89:11
13	3-Thienyl	5	0.1	72	13l	23	83:17	84:16
14	5-Br-2-Furyl	5	0.1	20	13m	62	81:19	85:15

^a Isolated yields of *syn* and *anti* isomers.

^b Determined by ¹H NMR analyses of crude reaction mixture.

^c Determined by chiral HPLC analyses.

^d Determined after conversion to methyl ester.

In conclusion, we have developed the first reported enantio- and diastereoselective decarboxylative aldol addition reaction between α -amido MAHOs and aldehydes for the synthesis of *anti*- β -hydroxy- α -amino esters. Our novel bifunctional organocatalyst mediated reactions in moderate to excellent yield with electron deficient aldehydes, and with high selectivity. While results were less impressive with deactivated aldehydes, this work promises to lead to further advances in the area of organocatalyzed decarboxylative reactions and sustainable catalysis, and is an area we continue to pursue as part of our research theme.

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Supporting Information

Supporting Information for this article is available online at <http://>

References and Notes

- (1) (a) Review: Zhang, Y.; Farrants, H.; Li, X. *Chem. Asian J.* **2014**, *9*, 1752. (b) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Hirata, Y.; Yamasu, T.; Sasaki, T.; Ohizumi, Y. *Experientia* **1988**, *44*(9), 800. (c) Nakada, N.; Shimada, H.; Hirata, T.; Aoki, Y.; Kamiyama, T.; Watanabe, J.; Arisawa, M. *Antimicrob. Agents Chemother.* **1993**, *37*(12), 2656. (d) Fenteany, G.; Schreiber, S. L. *J. Biol. Chem.* **1998**, *273*, 8545. (e) Chaudhari, P. N.; Wani, K. S.; Chaudhari, B. L.; Chincholkar, S. B. *Appl. Biochem. Biotechnol.* **2009**, *158*(1), 231. (f) Nakamura, H.; Tsukano, C.; Yasui, M.; Yokouchi, S.; Igarashi, M.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2015**, *54*(10), 3136.
- (2) (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, N. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (b) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 882. (c) Hamada, Y.; Koseki, Y.; Fujii, T.; Maeda, T.; Hibino, T.; Makino, K. *Chem. Commun.* **2008**, 46, 6206. (d) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274.
- (3) (a) Qiu, L.; Guo, X.; Jing, C.; Ma, C.; Liu, S.; Hu, W. *Chem. Commun.* **2016**, *52*, 11831. (b) Qian, Y.; Jing, C.; Liu, S.; Hu, W. *Chem. Commun.* **2013**, *49*, 2700.
- (4) (a) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192. (b) Chen, X.; Zhu, Y.; Qiao, Z.; Xie, M.; Lin, L.; Liu, X.; Feng, X. *Chem. Eur. J.* **2010**, *16*, 10124. (c) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.*, **2015**, *54*, 6236.
- (5) (a) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4542. (b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685. (c) Thayumanavan, R.; Tanaka, F.; Barbas, III, C. F. *Org. Lett.* **2004**, *6*, 3541.
- (6) (a) Singjunla, Y.; Baudoux, J.; Rouden, J. *Org. Lett.* **2013**, *15*, 5770. (b) Baudoux, J.; Lefebvre, P.; Legay, R.; Lasne, M.-C.; Rouden, J. *Green Chem.*, **2010**, *12*, 252.
- (7) Blaquiére, N.; Shore, D. G.; Rousseaux, S.; Fagnou, F. *J. Org. Chem.* **2009**, *74*, 6190.
 - (a) Review: Nakamura, S. *Org. Biomol. Chem.*, **2014**, *12*, 394. (b) Orlandi, S.; Benaglia M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747.
 - (c) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284. (d) Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 2976. (e) Li, X.-J.; Xiong, H.-Y.; Hua, M.-Q.; Nie, J.; Zheng, Y.; Ma, J.-A. *Tetrahedron Lett.* **2012**, *53*, 2117. (f) Zhong, F.; Yao, W.; Dou, X.; Lu, Y. *Org. Lett.*, **2012**, *14*, 4018. (g) Bae, H. Y.; Sim, J. H.; Lee, J.-W.; List, B.; Song, C. E. *Angew. Chem. Int. Ed.*, **2013**, *52*, 12143. (h) Duan, Z.; Han, J.; Qian, P.; Zhang, Z.; Yi, W.; Yi, P. *Beilstein J. Org. Chem.* **2014**, *10*, 969. (i) Wei, A.-J.; Nie, J.; Zheng, Y.; Ma, J.-A. *J. Org. Chem.* **2015**, *80*, 3766. (j) Bew, S. P.; Stephenson, G. R.; Rouden, J.; Ashford, P.-A.; Bourane, M.; Charvet, A.; Dalstein, V. M. D.; Jauseau, R.; Hiatt-Gipson, G. D.; Martinez-Lozano, L. A. *Adv. Synth. Cat.* **2015**, *357*, 1245. (k) Xu, F.; Xu, J.; Hu, Y.; Lin, X.; Wu, Q. *RSC Adv.* **2016**, *6*, 7682. (l) Ren, N.; Nie, J.; Ma, J.-A. *Green Chem.* **2016**, *18*, 6609.
 - (8) Saadi, J.; Wennemers, H. *Nat. Chem.* **2016**, *8*, 276.
 - (9) See Supporting Information for details. See also our contributions, (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.*, **2003**, *125*, 12672. (b) Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11114. (c) Hayama, N.; Azuma, T.; Kobayashi, Y.; Takemoto, Y. *Chem. Pharm. Bull.* **2016**, *64*, 704.
 - (10) *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis* Song, C. E., Ed.; Wiley-VCH, Weinheim, **2009**, and references therein.
 - (11) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.
 - (12) **Representative Procedure for the Enantioselective Decarboxylative Aldol Reaction:** To a stirred solution of **1j** (0.05 mmol) in (0.5–1.0 mL) of dry CPME at 10–15 °C, was added *o*-nitrobenzaldehyde (37.8 mg, 0.25 mmol), catalyst **11** (5.2 mg, 20 mol%), and pentafluorobenzoic acid (2.1 mg, 20 mol%). The mixture was stirred at the same temperature for 48 h, before being directly purified by silica gel column chromatography (hexane/AcOEt) to give the *anti*- β -hydroxy- α -amino acid **13a**.
Phenyl (2S,3S)-2-[(9H-fluoren-9-yl)methoxycarbonyl]amino-3-hydroxy-3-(2-nitrophenyl)propanoate (13a): ¹H NMR (CDCl₃, 400 MHz) δ : 8.03 (d, *J* = 6.4 Hz, 1H), 7.91–7.90 (m, 1H), 7.75 (d, *J* = 6.4 Hz, 2H), 7.66 (t, *J* = 6.2 Hz, 1H), 7.55–7.47 (m, 3H), 7.40–7.34 (m, 5H), 7.30–7.21 (m, 3H), 7.00 (d, *J* = 6.0 Hz, 2H), 5.85–5.80 (m, 2H), 5.02–4.99 (m, 1H), 4.24–4.34 (m, 2H), 4.19–4.15 (m, 1H), 3.69 (bs, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 168.9, 156.1, 150.0, 147.8, 143.5, 141.2, 135.2, 133.7, 129.5, 129.4, 129.1, 127.7, 127.1, 126.2, 125.0, 124.8, 121.1, 119.9, 70.4, 67.4, 59.4, 46.9; IR (ATR): 3401, 1763, 1703, 1522 cm⁻¹; HRMS (ESI): calcd. for C₃₀H₂₄N₂NaO₇ [M+Na]⁺ 547.1476, found 547.1464; HPLC [Chiralpak AD, hexane/2-propanol = 80/20, 0.8 mL/min, λ = 254 nm, retention times: (major) 34.1 min (minor) 24.7 min]. products.