Environmentally benign metal-free decarboxylative aldol and Mannich reactions

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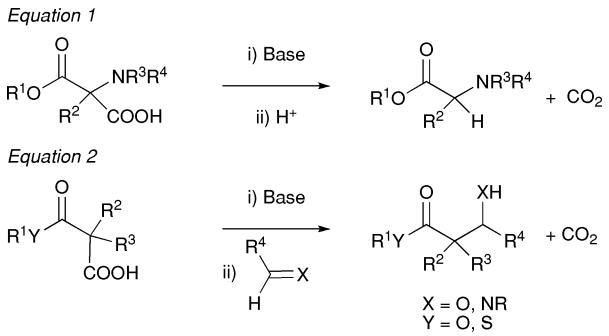
Received 31st July 2009, Accepted 15th October 2009
First published as an Advance Article on the web 18th November 2009
DOI: 10.1039/b915681j

Aiming at the development of green and efficient C–C bond formations (aldol and Mannich reactions), the decarboxylative nucleophilic addition of malonic acid half ester to imines or aldehydes under mild metal-free conditions was studied. A careful control of the temperature and the appropriate choice of the organic base allowed us to obtain β-amino esters or β-hydroxy esters including α-substituted and α,α-disubstituted ones in moderate to excellent yields. ^{1}H NMR monitoring of the reaction unveiled two distinct mechanisms depending on the hemimalonate used. With the unsubstituted substrate, a carboxylic acid intermediate was isolated upon acid quench resulting from the nucleophilic addition of the putative enol carboxylate anion of the hemimalonate to imines/aldehydes before CO_2 loss. With substituted hemimalonates, the reaction likely involved an enolate which then added to imines/aldehydes or was competitively protonated. According to the base used, the reaction can be carried out either under solvent free-conditions or in an ionic liquid under mild conditions.

Introduction

The development of organic reactions based on the twelve principles of Green Chemistry is one of the most important issues in today's scientific community.[1] In recent years, much attention has been paid to the development of organocatalysis,[2] an eco-friendly and cost-effective concept well-suited for industrial applications, especially when metal traces is of real concern (pharmaceutical industry). Organocatalyzed aldol[3] and Mannich[4] reactions based on enamine reactive intermediates, two organic economical-atom transformations, have been widely studied. With the exception of a direct aldol reaction mediated by silyl trifluoromethanesulfonate in the presence of diisopropylethylamine,[5] the available methods for a direct metal-free aldol reaction of esters are nearly non existent because of the lower enolization ability of esters compared with that of ketones. Organocatalytic routes using ester and aldehyde partners involved ketene (thio)acetals as ester equivalents and chiral phosphoramides or pyridine *N*-oxides,[6] oxazaborolidinone derivatives[7] or triarylcarbenium ions[8] as catalysts. An aldol reaction was also observed in DMSO.[9] The formation of β-amino esters in organocatalyzed Mannich type reactions has been studied much more.[4] Usually a protected imine (or an equivalent of imine) reacts with a dialkyl malonate,[10] or a ketene acetal. Although efficient, these approaches require more than one step. Given their valuable roles as versatile building blocks in the synthesis of natural products or compounds of biological interest,[11] the development of an eco-friendly synthesis of β-hydroxy esters and to a lesser extent to β-amino esters is rather desirable.

Recently, we showed[12] that enantioselective decarboxylative protonation[13] of α-amino substituted malonic acid half esters is an attractive route to enantioenriched α-amino acids due to the mild conditions and the general applicability of the reaction. As part of an ongoing project concerning the metal-free synthesis of functionalized carbonyl compounds[14] we envisaged the use of the organic base-catalyzed decarboxylation of malonic acid half esters (or "hemimalonates") as a mild and convenient procedure to generate an enolate of ester with its subsequent reaction with an electrophile (imines or aldehydes) (Scheme 1). The simple malonic acid half ethyl ester **1a** is a commercially available stable β-acid ester which can be easily made quantitatively from the very cheap diethyl malonate or the potassium salt of ethyl hemimalonate. Recently published work[15] prompted us to describe thereafter our results focused on the following practical issues: (i) high conversion of the reagents under stoichiometric ratios, (ii) metal-free conditions, (iii) eco-friendly medium, (iv) cost-effectiveness, (v) low energy demand, (vi) easy work-up.



Scheme 1 Decarboxylative C–C bond forming reaction.

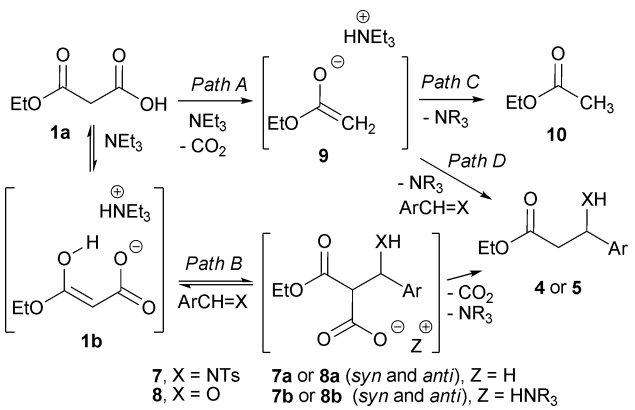
Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, ENSICAEN, Université de Caen Basse Normandie, 6, Bd Maréchal Juin, 14050 Caen, France. E-mail: jacques.rouden@ensicaen.fr; Fax: +33 23145 2877; Tel: +33 23145 2893

Results and discussion

Decarboxylative C–C bond forming reactions from malonic acid half esters usually required the generation of a magnesium salt[16,17] or the formation of a lithium enolate.[18] Under basic conditions, *N*-acetyl serine esters were successfully prepared from acetamido hemimalonate[19] whereas a decarboxylative Claisen reaction was observed[20] with activated malonic acid half esters. The related Doebner–Knoevenagel reaction was studied both from the mechanistic[21] and practical[22] points of view. Using a well-designed malonic acid half ester,[23] Ohta *et al.*[24] demonstrated that arylmalonate decarboxylase catalyzed an intramolecular decarboxylative aldol reaction.[25]

While transition metal catalyzed decarboxylation of β-keto acids and esters is well known, particularly in aldol and Michael additions or in allylic substitutions,[26] only a few involve hemimalonates. Based on a biomimetic approach and on the enhanced acidity of a thioester function relative to simple esters, the groups of Cozzi[27] and Shair[28] developed the aldol-decarboxylation reaction of aldehydes and malonic- or methylmalonic acid half thioesters in the presence of a copper (II) complex. Ricci *et al.*[29] described the first organocatalytic asymmetric decarboxylative nucleophilic addition of malonic acid half thioesters to imines. This work led us to test the feasibility of a decarboxylative C–C bond forming reaction using hemimalonate **1a** as a straightforward available substrate.

Based on literature precedents, the mechanism of the reaction (Scheme 2) can involve the formation of enolate **9** (path A)[29] prior to protonation (path C) or reaction with imine **2a** (path D). Direct addition of imine **2a** to malonic acid half ester salt **1b** (path B)[15,22,28] can also be envisaged prior to decarboxylation of salt **7** (or **8**).



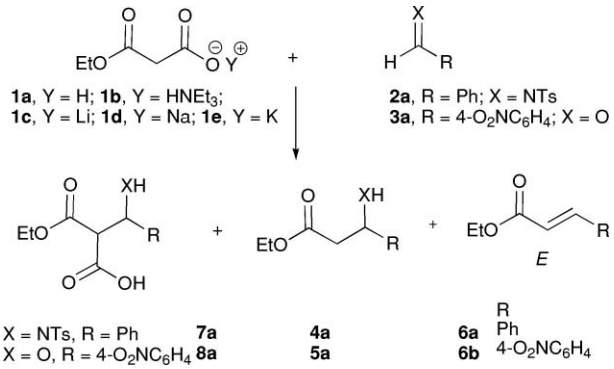
Scheme 2 Mechanistic hypothesis for the formation of the products.

When **1a** was mixed with imine **2a** in THF at 65 °C for 15 h but without any base, no reaction occurred. Adding a tertiary amine (NEt_3)[30] in a 1:1:2 imine/organic base/hemimalonate **1a** molar ratio, imine **2a** was completely transformed at room temperature affording β-amino ester **4a** in 68% yield (Scheme 3). The same reaction was performed with the preformed ammonium salt **1b** or with the salts **1c-1e**. The results, presented in Table 1, clearly show the benefits of using an organic ammonium countercation in these reactions. A mixture of the expected product **4a** was formed beside the non-decarboxylated compound **7a** (characterized in-situ as its ammonium salt **7b**) and the Knoevenagel–

Table 1 Influence of the cation on the outcome of the reaction of imine **2a** and hemimalonates **1b-e**

			Products, ratio[b]		
Entry[a]	Y	Compound **1**	**7a**	**4a**	**6a** (*E*)
1	$HNEt_3$	**b**	0	100	0
2	Li	**c**	43	22	35
3	Na	**d**	57	21	22
4	K	**e**	39	46	15

[a] Conditions: salt **1** (1.55 mmol, 200 mg), imine **2a** (1 equiv), THF (0.1 M), room temperature, 24 h. Conversion: 100%. [b] From ^1H NMR after work-up.



Scheme 3 Reaction of hemimalonates with electrophiles.

Doebner product **6a** with the inorganic salts **1c-1e**, whereas the ammonium salt **1b** afforded exclusively the β-amino derivative **4a** (Table 1, comparison of entry 1 with entries 2-4).

In the following experiments, NEt_3 was chosen as the organic base for the optimization of the parameters. Several solvents were screened in the reaction carried out at 45 °C for 48 h. In dichloromethane, carbon tetrachloride, toluene or dioxane, the conversion was low (less than 50%) whereas the expected product **4a** was formed in satisfactory yields in THF, DMF or acetonitrile (Table 2). Decreasing the amount of hemimalonate **1a** had no significant influence (comparisons between entry 4).

Increasing the concentration of the imine **2a** to 1.8 mol.L^{-1} improved the yields for the reaction carried out in DMF (comparison of entries 4 and 5) and allowed the reaction to be complete in 3 h in THF at 45 °C. The highest yield (66%) with the lowest amounts of solvent and substrate **1a** were thus obtained

Table 2 Reaction of ethyl hemimalonate **1a** with imine **2a**

Entry	**2a**[a] conc.	**1a** equiv	NEt_3 equiv	Solvent	t (h)	**4** yield[b]%
1	0.1	1	1	THF	24	52-57
2	0.1	1.3	0.5	THF	24	49
3	0.1	1.3	0.25	THF	24	33
4	1.8	2 or 1	1	DMF	24	60-66
5	0.1	2	0.20	DMF	48	47
6	1.8	1.3	0.20	DMF	48	57
7	0.1	2	1	CH_3CN	15	67
8	1.8	1	1	CH_3CN	48	56

[a] Conditions: hemimalonate **1a**, imine **2a** (100 mg, 0.386 mmol), molecular sieves (4 A°) and NEt_3 were stirred at 45 °C. [b] Isolated yields. Conversion of imine **2a**: 100%.

in DMF (entry 4). Working under solvent-free conditions gave only degradation products.

The reaction was attempted under catalytic conditions (Table 2, entries 2, 3, 5, 6). In THF (0.1 M), the yield of **4a** decreased with the amine loading (entries 2 and 3). However in DMF, under the standard conditions (1.8 M, entry 4) but with a longer reaction time (48 h) and 0.2 equiv of base, reaction of imine **2a** with hemimalonate **1a** (entry 6) afforded β-amino ester **4a** in just slightly lower yield than that obtained under stoichiometric conditions.

Next, ^{1}H NMR monitoring of the reaction at room temperature of malonic acid half ester **1a** with imine **2a** as a function of time clearly demonstrated the formation of carboxylic acid intermediate **7** as a 2/1 mixture of diastereoisomers **A** (*anti or syn*) and **B** (*syn or anti*) (Fig. 1). The experiments showed the rapid disappearance of imine **2a** concomitant with the dual formation of **A** and **B**, then product **4a** appeared after 90 min upon the slow decarboxylation of these intermediates. Whatever the conditions and all along the progress of the reaction, the ratio of both diastereoisomers stayed constant. This could be explained by the reversibility[15] of the malonate nucleophilic addition on imines, reflecting thus the relative stability of intermediates **A** and **B**.

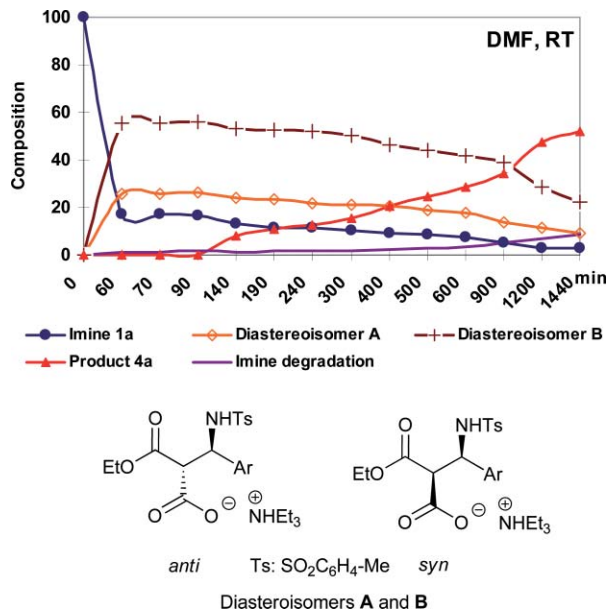


Fig. 1 Monitoring of the reaction mixture **1a**, imine **2a**, NEt_3 in DMF-d_7 as a function of time at room temperature.

Having demonstrated the feasibility of forming a C–C bond from decarboxylative Mannich type reaction of malonic acid half ester **1a**, we attempted a decarboxylative aldol reaction using 4-nitrobenzaldehyde **3a** and hemimalonate **1a** (Table 3). In the presence of NEt_3 or DMAP (1 equiv) in DMF or acetonitrile (entries 1-4), the reaction of aldehyde **3a** with hemimalonate **1a** led exclusively to the expected aldol product **5a** in satisfactory yields. Similar results were obtained when 1,8-bis(dimethylamino)naphthalene (proton sponge "PS") was used in acetonitrile (entry 6) whereas the Knoevenagel–Doebner

Table 3 Reaction of hemimalonate **1a** with 4-nitrobenzaldehyde **3a**

Entry	Base[a]	Solvent	Ratio **5a**/**6b**/**3a**	**5a** Yield[b]%
1	NEt_3	DMF[c]	100/0/0	78
2	NEt_3	MeCN[d]	100/0/0	85
3	DMAP	DMF[c]	100/0/0	70
4	DMAP	MeCN[d]	100/0/0	70
5	PS[e]	DMF[c]	76/24/0	50
6	PS	MeCN[d]	90/0/10	82
7	NEt_3	[BMIM] [PF_6]	100/0/0	72[g]
8	NEt_3	no[f]	100/0/0	85
9	NEt_3	no[f]	87/0/13	72[g]

[a] Reagents: hemimalonate **1a** (90 mg, 0.66 mmol), aldehyde **3a** (100 mg, 0.66 mmol, 1.8 M in the solvent), base (1 equiv). [b] Isolated yields with 100% conversion. [c] 24 h at 20 °C then 15 h at 60 °C. [d] 15 h at 80 °C. [e] PS: 1,8-bis(dimethylamino)naphthalene (Proton Sponge). [f] 2 h at 20 °C then 15 h at 60 °C. [g] Reaction carried out on a gram scale.

product **6b** was a side product in the reaction carried out in DMF (entry 5). Polar solvents being required for the reaction, we attempted the decarboxylative aldol reaction in the hydrophobic butyl methyl imidazolium hexafluorophosphate [BMIM][PF_6], a room temperature ionic liquid (RTIL). Indeed, due to their properties (high polarity, no vapor pressure, high thermal stability), RTILs are environmentally friendly substitutes for conventional organic solvents. Under the conditions described in entry 7, compound **5a** was isolated in 72% yield.

It is worth noting that the reaction proceeded in high yield in the absence of solvent. The isolation of the pure product required only an acid-base work-up (entry 8). The same reaction performed on a gram scale afforded product **5a** in a slightly lower yield due to the incomplete conversion of the starting material (entry 9).

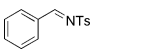
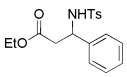
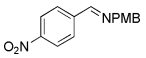
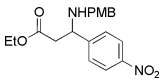
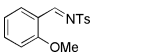
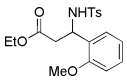
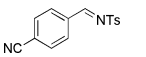
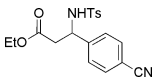
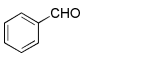
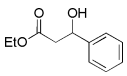
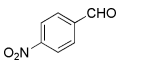
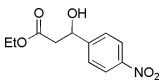
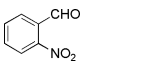
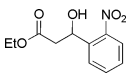
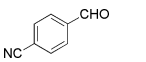
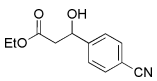
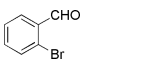
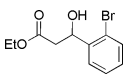
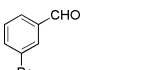
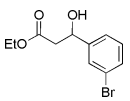
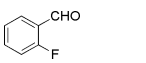
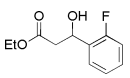
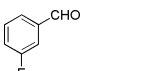
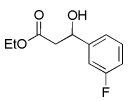
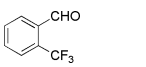
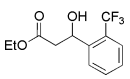
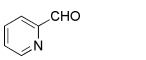
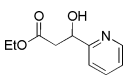
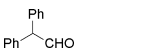
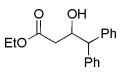
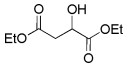
Attempts to carry out the reaction under catalytic conditions of base gave no satisfactory results. A mixture of aldol **5a**, unsaturated ester **6b** and unreacted aldehyde **3a** was formed.

From the products observed in those reactions, Path B of the mechanism was mainly operating with unsubstituted hemimalonate at room temperature. The unstable carboxylic acid **8a**, as a mixture of two diastereoisomers, was isolated and characterized. Such an intermediate was postulated in the condensation of β-ketoacid salts with aldehydes.[31]

The scope of the reaction was then examined changing the electrophilic partner of hemimalonate **1a**. The reactions of **1a** with various aldehydes and imines were carried out in DMF or acetonitrile in the presence of NEt_3. The results are shown in Table 4. Due to the instability of the imines used, average yields were obtained for the corresponding Mannich products (entries 1-4). Aldehydes bearing an electron-withdrawing group led to the aldol products with good yields (entries 6-9). Yields from halogenated aldehydes were slightly lower (entries 8-13). Benzaldehyde, pyridine carboxaldehyde, diphenylethanal gave moderate results, due to an incomplete conversion (entries 5, 14, 15). No reaction was observed with 4-methoxybenzaldehyde and *n*-hexanal (data not shown).

Finally, the reaction was examined with α-substituted malonic acid half esters **11a-c**, disubstituted α-methyl-α-phenyl hemimalonate **11d** and α-acetamido-α-benzyl hemimalonate **11e**. The first attempts to carry out the reaction of α-phenylmalonate

Table 4 Reaction of hemimalonate **1a** with imines and aldehydes

Entry	Electrophile	Product		Yields A[a]	(%) B[b]
1			**4a**	77	84
2			**4b**	47	52
3			**4c**	55	59
4			**4d**	51	49
5			**5a**	nr	26
6			**5b**	78	85
7			**5c**	81	86
8			**5e**	81	81
9			**5f**	79	73
10			**5g**	70	67
11			**5h**	72	66
12			**5i**	57	68
13			**5j**	80	75
14			**5k**	39	52
15			**5l**	38	48
16	EtO_2C-CHO		**5n**	62	63

[a] Reaction carried out in DMF (imine or aldehyde: 1.8 M), NEt_3 (1 equiv), room temperature for 24 h then 60 °C for 15 h. [b] Reaction carried out in acetonitrile (imine or aldehyde: 1.8 M), NEt_3 (1 equiv), 80 °C, 15 h.

11a with 4-nitrobenzaldehyde in the presence of NEt_3 in acetonitrile were unsuccessful. The sole product of the reaction was ethyl phenylacetate, resulting from the competitive protonation of the intermediate enolate (path A then C of the mechanistic hypothesis, Scheme 2).

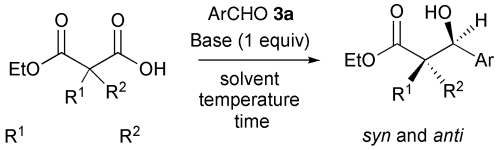
Such an enhanced reactivity of ethyl α-phenylmalonic acid half ester towards the decarboxylation was observed in the sulfenylation of the hemiester **1a**.[32] In order to avoid the fast protonation of the enolate, NEt_3 was substituted by proton sponge [1,8-bis(dimethylamino)naphthalene] as a better proton scavenger. Gratifyingly, this base allowed the decarboxylative aldolisation reaction at 0 °C in acetonitrile and **12a** was isolated in 76% yield (Table 5, entry 1). In DMF, the reaction was less efficient (entry 2). The reaction attempted in [BMIM][PF_6] did not improve the yield of **12a**, and 10% of the side-product ethyl phenylacetate was formed (entry 3).

The reaction involving the less reactive substituted derivatives **11b** and **11c** required heating in DMF to achieve the decarboxylation and afforded the hydroxy esters **12b** and **12c** in 68% and 77% yields respectively (entries 4, 5). Hemimalonates **11d** and **11e** bearing a quaternary carbon were subjected to the decarboxylative aldol reaction under different conditions of bases and solvents. Whereas the reaction of hemimalonate **11d** and 4-nitrobenzaldehyde **3a** in the presence of NEt_3 led only to the protonated side product (ethyl 2-phenylpropanoate, data not shown), the proton sponge mediated reaction of **3a** with **11d** or **11e** in DMF, afforded compound **12d** or **12e** in 39% or 78% yields respectively (entries 6, 9). Working in [BMIM][PF_6] at room temperature improved significantly the yield of **12d** (entry 7) whereas **12e** was formed in 51% yield in this solvent. Although these yields seem moderate, the reaction allowed the formation of a quaternary carbon and of two consecutive stereogenic centers under very mild conditions. Due to the disubstituted nature of the starting material, only the mechanistic hypothesis described by Path A then C on Scheme 2 is operating, *i.e.* the decarboxylation occurred first generating the enolate which was then trapped by the aldehyde before the protonation took place.

Conclusion

We have demonstrated that, using a metal-free procedure, the simple commercially available malonic acid half ethyl ester **1a** was an efficient reagent for the formation of β-hydroxy esters and β-amino esters from aryl aldehydes and arylimines *via* decarboxylative aldol and Mannich type reactions respectively. This one-step organic base-mediated procedure, possible under catalytic conditions in some cases, can replace favourably the well-known two-reaction sequence involving nucleophilic addition of malonate diester followed by a subsequent decarboxylation reaction. The simplicity of this synthetic approach which can be carried out in an open flask, even under solvent-free conditions or in ionic liquids, may render it applicable on a large scale. Depending on the malonyl starting material used (substituted or not), two different mechanisms can be involved which may dictate the choice of the organic base used. With α-substituted and α,α-disubstituted hemimalonates, two consecutive stereogenic centers are created, including a quaternary carbon with the later substrates.

Table 5 Decarboxylative aldolisation of α-substituted and disubstituted malonic acid hemi esters



R^1	R^2		
Ph	H	**11a**	**12a**
Bn	H	**11b**	**12b**
CH_2COPh	H	**11c**	**12c**
Ph	Me	**11d**	**12d**
NHCOMe	Bn	**11e**	**12e**

Entry	Acid[a]	Base	Conditions: Solvent, Temp Time	Product **12** yield[b] %	*syn*/*anti*[c] ratio%
1	**11a**	PS	MeCN, 0 °C 18 h	**12a**, 76	44/56
2	**11a**	PS	DMF, 0 °C 60 h	**12a**, 43	45/55
3	**11a**	PS	[BMIM][PF_6], 20 °C 48 h	**12a**, 65	50/50
4	**11b**	NEt_3	DMF, 0 °C 60 h, then 60 °C 5 h	**12b**, 68	50/50
5	**11c**	NEt_3	DMF, 0 °C 60 h, then 60 °C 5 h	**12c**, 77	34/66
6	**11d**	PS	DMF, 20 °C 48 h	**12d**, 39	50/50
7	**11d**	PS	[BMIM][PF_6] 20 °C 48 h	**12d**, 56	50/50
8	**11e**	PS	[BMIM][PF_6] 20 °C 48 h	**12e**, 51	50/50
9	**11e**	PS	DMF, 20 °C 48 h	**12e**, 78	50/50

[a] Acid **11** (1.1 equiv), base (1 equiv), aldehyde **3a** (1 equiv). [b] Isolated yield. [c] Ratio in the crude product, from ^{1}H NMR spectra.

Experimental

General

Acetonitrile (MeCN), tetrahydrofuran (THF), toluene and dichloromethane were dried with a Pure-Solv™ 400 Solvent Purification System. Dimethylformamide (DMF) and triethylamine (Et_3N) were distilled from CaH_2 under a stream of nitrogen prior to use. Commercially available compounds (aldehydes, tosylamine, *p*-methoxybenzylamine, benzyl chloride, methyl iodide, 1,8-bis(dimethylamino)naphthalene, diethyl malonate, diethyl α-phenylmalonate, and diethyl α-acetamidomalonate) were used as received. *N*-Tosylimines and *N*-4-methoxybenzylimine precursor of compound **4b** were prepared according Kim *et al.*[33] Diethyl phenacylmalonate,[34] diethyl 2-methyl, 2-phenylmalonate,[35] and diethyl 2-(*N*-acetamido)-2-benzylmalonate[36] were prepared by alkylation of diethyl malonate, diethyl α-phenylmalonate, and diethyl α-acetamidomalonate respectively. Ethyl hemimalonates were obtained by selective hydrolysis[37] of the corresponding dialkylmalonates and their spectroscopic properties were in good agreement with those reported for **1a**,[37] **11a**,[37] **11b**,[38] **11c**,[39] **11d**.[40,41] The spectral data of the known products **4a**,[42] **5a**,[43] **5b**,[44] **5c**,[44] **5e**,[45] **5f-5i**,[44] **5l**,[46] **5n**,[47] were in agreement with literature data.

Characterization of the intermediates, ammonium salt 7b and carboxylic acid 8a

Reaction between malonate 1a and imine 2a. Freshly distilled triethylamine (28 μL, 0.2 mmol) was added to a solution of malonic acid half ethyl ester **1a** (32 mg, 0.2 mmol) in dried DMF-d_7 (1 mL). In a NMR tube, imine **2a** (31 mg, 0.12 mmol) was weighed then 0.6 mL of the previous solution was added to start the reaction. The ammonium salt **7b** of carboxylic acid intermediate was characterized in-situ by ^{1}H NMR (–20 °C) after a few minutes in the form of two diastereomers. ***First diastereomer:*** ^{1}H NMR (500 MHz, DMF-d_7) δ 1.18 [t, 3 H, $^3J_{HH}$ = 7.5 Hz, CH_3(Et)], 1.19 (t, 9 H, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.30 [s, 3 H, CH_3(Ar)], 3.01 (q, 6 H, $^3J_{HH}$ = 7.5 Hz, CH_2), 3.62 (d, 1 H, $^3J_{HH}$ = 10.0 Hz, CH), 4.04 [q, 2 H, $^3J_{HH}$ = 7.5 Hz, CH_2(Et)], 5.06 (t, 1 H, $^3J_{HH}$ = 9.5 Hz, CH), 7.06 (m, 3 H, H_{Ar}), 7.12 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, H_{Ar}), 7.28 (m, 2 H, H_{Ar}), 7.43 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, H_{Ar}), 8.10 (d, 1 H, $^3J_{HH}$ = 9.5 Hz, NH). ^{13}C NMR (125 MHz, DMF-d_7) δ 8.5 (CH_3), 13.9 [CH_3(Et)], 20.6 (CH_3), 45.0 (CH_2), 58.5 (CH), 60.0 (CH_2), 62.5 (CH), 126.6, 127.4, 128.2, 128.9, 139.5, 140.6, 142.0 (C_{Ar}), 169.1 (C=O), 169.5 (C=O). ***Second diastereomer:*** ^{1}H NMR (500 MHz, DMF-d_7) δ 0.95 [t, 3 H, $^3J_{HH}$ = 7.0 Hz, CH_3(Et)], 1.19 (t, 9 H, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.39 [s, 3 H, CH_3(Ar)], 3.01 (q, 6 H, $^3J_{HH}$ = 7.5 Hz, CH_2), 3.45 (d, 1 H, $^3J_{HH}$ = 9.5 Hz, CH), 3.81 [ABX_3 syst., 2 H, CH_2(Et)], 4.62 (s, 1 H, $^3J_{HH}$ = 9.5 Hz, CH), 7.19 (m, 3 H, H_{Ar}), 7.29 (m, 2 H, H_{Ar}), 7.31 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, H_{Ar}), 7.57 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, H_{Ar}). ^{13}C NMR (125 MHz, DMF-d_7) δ 8.5 (CH_3), 13.5 [CH_3(Et)], 20.6 (CH_3), 45.0 (CH_2), 58.0 (CH), 59.8 (CH), 59.9 (CH_2), 127.1, 127.2, 127.8, 128.1, 129.4, 138.1, 140.6, 142.7 (C_{Ar}), 168.9 (C=O), 171.0 (C=O).

Reaction between malonate 1a and aldehyde 3a. Freshly distilled triethylamine (1.06 mL, 7.6 mmol) was added to a solution of malonic acid half ethylester **1a** (1 g, 7.6 mmol) in CH_2Cl_2 (11 mL). Para-nitrobenzaldehyde **3a** (1.37 g, 9.1 mmol) was added to the solution and the reaction was stirred at room temperature for 20 h. The mixture was quenched with HCl (1 N) and extracted with CH_2Cl_2 to afford 0.95 g of the unstable carboxylic acid intermediate **8a** (49% yield) which was rapidly characterized by ^{1}H and ^{13}C NMR shortly after as a mixture of two diastereomers.

First diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 [t, 3 H, *J* = 7.2 Hz, CH_3(Et)], 3.74 (d, 1 H, *J* = 7.6 Hz, CH), 3.99-4.07 [m, 2 H, CH_2(Et)], 5.35 (d, 1 H, *J* = 7.6 Hz, CH), 7.55 (d, 2 H, *J* = 8.5 Hz, H_{Ar}), 8.14 (d, 2 H, *J* = 8.5 Hz, H_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 [CH_3(Et)], 59.3 (CH), 62.0 [CH_2(Et)],

71.9 (CH), 123.5, 127.6, 147.5, 147.8 (C_{Ar}), 167.3 (C=O), 170.8 (C=O). ***Second diastereomer:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 3.79 (d, 1 H, J = 5.8 Hz, CH), 4.07-4.14 [m, 2 H, CH_2(Et)], 5.41 (d, 1 H, J = 5.8 Hz, CH), 7.55 (d, 2 H, J = 8.5 Hz, H_{Ar}), 8.14 (d, 2 H, J = 8.5 Hz, H_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 [CH_3(Et)], 58.7 (CH), 62.2 [CH_2(Et)], 71.7 (CH), 123.5, 127.3, 147.5, 147.9 (C_{Ar}), 168.3 (C=O), 169.9 (C=O).

Typical procedures

The organic base (1 equiv) was added to a stirred mixture of the aldehyde or imine (1 equiv), the malonic acid half ethylester (1.1 equiv) and the solvent. This mixture was stirred for a given time at a chosen temperature. In procedures **A-D**, the volatile compounds were removed under vacuum. The residue was diluted in ether/dichloromethane (1:1), washed with aqueous saturated $NaHCO_3$, then with HCl (1 N) and dried over $MgSO_4$. The solvents were removed under vacuum, and the residue was purified by silica-gel column chromatography to give the expected product.

Procedure	Base	Solvent	Temperature and time
A	NEt_3	DMF	*cf.* Table 4 and Table 5 (entries 4-5).
B	NEt_3	MeCN	80 °C, 15 h
C	PS	DMF MeCN	*cf.* Table 3 entries 5, 6 and Table 5, entries 1-3, 6-9.
D	NEt_3	no	20 °C, 2 h then 60 °C, 15 h
E	PS	[BMIM][PF_6]	20 °C, 48 h

In Procedure **E**, The reaction mixture was extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography.

Ethyl 3-*N*-[(4-methoxyphenyl)methyl]-3-(4-nitrophenyl)propanoate 4b (Procedure B). Under nitrogen and in the presence of molecular sieves (4Å). [69 mg, 52% yield from imine (99 mg)]. R_f 0.29 (Cyclohexane/AcOEt = 85:15). White solid (mp 105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 2.77 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 15.2, J_{AX} = 7.6 Hz, $CH_2(H_a)$], 2.82 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 15.2, J_{BX} = 7.6 Hz, $CH_2(H_b)$], 3.70 (s, 3 H, OMe), 4.12 [q, 2 H, J = 7.2 Hz, CH_2(Et)], 4.83 (dd, 1 H, J = 5.6, 7.6 Hz, CH), 6.46 (d, 2 H, J = 9.2 Hz, H_{Ar}), 6.69 (d, 2 H, J = 9.2 Hz, H_{Ar}), 7.56 (d, 2 H, J = 8.8 Hz, H_{Ar}), 8.18 (d, 2 H, J = 8.8 Hz, H_{Ar}).^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 [CH_3(Et)], 26.9 (CH_2), 43.3 (MeO), 55.5 (CH), 61.1 [CH_2(Et)], 114.8, 115.2, 124.0, 127.4, 140.1, 147.3, 150.2, 153.7 (C_{Ar}), 170.6 (CO). IR (neat) 3385 (N-H), 1726 (C=O), 1605, 1509, 1342, 1234, 1177, 1031 cm^{-1}. HRMS (ESI) Calcd for $C_{18}H_{21}N_2O_5$ (MH^+): 345.1450, Found: 345.1445; MS (ESI) m/z 345 (M + H)$^+$, 299, 257, 124, 123.

Ethyl 3-(4-methylphenylsulfonamido)-3-(2-methoxyphenyl)-propanoate 4c (Procedure B). Under nitrogen and in the presence of molecular sieves (4Å). [200 mg, 59% yield from imine (112 mg)]. White solid (mp 148 °C). R_f 0.28 (Cyclohexane/AcOEt = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 2.30 [s, 3 H, CH_3(Ts)], 2.76 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 15.2, J_{AX} = 7.2 Hz, $H_a(CH_2)$], 2.88 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 15.2, J_{BX} = 6.4 Hz, $H_b(CH_2)$], 3.75 [s, 3 H, CH_3(OMe)], 4.01 [m, 2 H, CH_2(Et)], 4.85 (m, 1 H, CH), 5.83 (dd, 1 H, J = 10.0 Hz, NH), 6.63 (dd, 1 H, J = 8.4, 0.8 Hz, H_{Ar}), 6.70 (dt, 1 H, J = 8.4 Hz, 0.8 Hz, H_{Ar}), 6.95 (dd, 1 H, J = 8.4 Hz, 0.8 Hz, H_{Ar}), 7.03 (d, 2 H, J = 8.3 Hz, H_{Ts}), 7.10 (dt, 1 H, J = 8.4 Hz, 0.8 Hz, H_{Ar}), 7.49 (d, 2 H, J = 8.3 Hz, H_{Ts}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 [CH_3(Et)], 31.4 [CH_3(Ts)], 40.4 (CH_2), 53.3 (CH), 55.2 [CH_3(OMe)], 60.7 [CH_2(Et)], 110.5, 120.5, 126.9, 128.9, 129.9, 129.3, 142.8, 156.3 (C_{Ar}), 170.5 (C=O). IR (neat) 3265 (N-H), 1733 (C=O), 1325, 1248, 1160 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{24}NO_5S$ (MH^+): 378.1375, Found: 378.1367; MS (ESI) m/z 378 (M + H)$^+$, 207.

Ethyl 3-(4-methylphenylsulfonamido)-3-(4-cyanophenyl)propanoate 4d (Procedure A). Under nitrogen and in the presence of molecular sieves (4Å). [70 mg, 51% yield from imine (110 mg)]. R_f 0.11 (Cyclohexane/AcOEt = 70:30). Yellow oil. ^{1}H NMR (400 MHz, ($CDCl_3$) δ 1.12 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 2.38 [s, 3 H, CH_3(Ts)], 2.70 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 16.0, J_{AX} = 5.6 Hz, $H_a(CH_2)$], 2.76 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 16.0, J_{BX} = 6.4 Hz, $H_b(CH_2)$], 4.00 [q, 2 H, J = 7.2 Hz, CH_2(Et)], 4.77 (m, 1 H, CH), 6.16 (d, 1 H, J = 8.0 Hz, NH), 7.17 (d, 2 H, J = 8.0 Hz, H_{Ar}), 7.26 (d, 2 H, J = 8.0 Hz, H_{Ar}), 7.47 (d, 2 H, J = 8.4 Hz, H_{Ar}), 7.57 (d, 2 H, J = 8.4 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 [CH_3(Et)], 21.5 [CH_3(Ts)], 40.6 (CH_2), 53.8 (CH), 61.3 [CH_2(Et)], 111.6 (C_{Ar}), 118.4 (CN), 127.1, 127.4, 129.6, 132.3, 137.2, 143.8, 144.8 (C_{Ar}), 170.3 (C=O). IR (neat) 3164 (N-H), 2227 (CN), 1712 (C=O), 1270, 1160 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{21}N_2O_4S$ (MH^+): 373.1222, Found: 373.1231 MS (ESI) m/z 373 (M + H)$^+$, 202, 172.

Ethyl 3-hydroxy 3-(2-trifluoromethylphenyl)propanoate 5j (Procedure A). [190 mg, 80% yield from aldehyde (157 mg)]. R_f 0.31 (Cyclohexane/AcOEt = 90:10). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 2.56-2.71 (m, 2 H, CH_2), 3.64 (d, 1 H, J = 2.9 Hz, OH), 4.19 [q, 2 H, J = 7.2 Hz, CH_2(Et)], 5.52-5.55 (m, 1 H, CH), 7.38 (t, 1 H, J = 7.5 Hz, H_{Ar}), 7.55-7.63 (M, 2 H, H_{Ar}), 7.82 (d, 1 H, J = 7.5 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 [CH_3(Et)], 43.4 (CH_2), 61.0 [CH_2(Et)], 65.9 (CH), 122.1, 125.4 (q, J = 5.8 Hz, CF_3), 126.6 (q, J = 22.9 Hz, CF_3) 127.6, 127.7, 132.4, 141.4 (C_{Ar}), 172.2 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.47. IR (neat) 3473 (O-H), 1717 (C=O), 1310, 1157, 1109 cm^{-1}. HRMS (ESI) Calcd for $C_{12}H_{14}O_3F_3$ (MH^+): 263.0895, Found: 263.0901. MS (ESI) m/z 263 (M + H)$^+$, 245, 203; Anal Calcd: C 54.96, H 5.00; Found: C 54.76; H 5.13.

Ethyl 3-hydroxy 3-(2-pyridinyl)propanoate 5k (Procedure B). [90 mg, 52% yield from aldehyde (96 mg)]. R_f 0.25 (Cyclohexane/AcOEt = 70:30). Light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 2.79 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 16.0, J_{AX} = 8.0 Hz, $CH_2(H_a)$], 2.94 [$\delta_{B(ABX)}$, 1 H, J_{AB} = 16.0, J_{BX} = 4.4 Hz, $CH_2(H_b)$], 4.17 [q, 2 H, J = 7.2 Hz, CH_2(Et)], 5.21 [$\delta_{X(ABX)}$, 1 H, J_{AX} = 8.0, J_{BX} = 4.4 Hz, CH), 7.26-7.29 (m, 1 H, H_{Ar}), 7.48 (d, 1 H, J = 8.0 Hz, H_{Ar}), 7.77 (dt, 1 H, J = 8.0 Hz, 2.0 Hz, H_{Ar}), 8.56 (d, 1 H, J = 4.0 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 [CH_3(Et)], 42.5 (CH_2), 60.7 [CH_2(Et)], 70.1 (CH), 120.3, 122.6, 136.9, 148.5, 160.8 (C_{Ar}), 171.9 (C=O). IR (neat) 3365 (O-H), 1718 (C=O), 1596, 1163, 1024 cm^{-1}. HRMS (ESI)

Calcd for $C_{11}H_{14}NO_3$ (MH^+): 196.0974, Found: 196.0975. MS (ESI) *m/z* 196 $(M + H)^+$, 178, 150, 132.

Ethyl 2-phenyl-3-hydroxy-3-(4-nitrophenyl)propanoate 12a (Procedure C). [50 mg, 77% yield from aldehyde (32 mg)]. R_f 0.29 (Cyclohexane/AcOEt = 80:20). Light brown oil. ***First diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, 3 H, J = 7.2 Hz, CH_3), 3.20 (bs, 1 H, OH), 3.81 (d, H, J = 6.0 Hz, CHPh), 4.02-4.13 (m, 2 H, CH_2), 5.42 (d, 1 H, J = 6.0 Hz, CHOH), 7.19-7.22 (m, 2 H, H_{Ar}), 7.28-7.41 (m, 3 H, H_{Ar}), 7.41 (d, 2 H, J = 8.8 Hz, H_{Ar}), 8.12 (d, 2 H, J = 8.8 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 58.8 (CPh), 61.4 (CH_2), 73.8 (COH), 123.3, 127.5, 128.2, 128.7, 129.2, 133.4, 147.5, 148.0 (C_{Ar}), 172.6 (C=O). ***Second diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3 H, J = 6.8 Hz, CH_3), 3.49 (d, 1 H, J = 4.0 Hz, OH), 3.78 (d, 1 H, J = 9.2 Hz, CHPh), 4.14-4.27 (m, 2 H, CH_2), 5.27 (dd, 1 H, J = 9.2 Hz, J = 4.0 Hz, CHOH), 7.02-7.05 (m, 2 H, H_{Ar}), 7.20-7.23 (m, 5 H, H_{Ar}), 8.03 (d, 2 H, J = 8.4 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 59.9 (CPh), 61.6 (CH_2), 75.7 (COH), 123.2, 127.5, 128.0, 128.4, 128.8, 134.5, 147.4, 148.0 (C_{Ar}), 173.1 (C=O). IR (neat) 3526 (O-H), 2984, 1705 (C=O), 1517, 1345 cm^{-1}. HRMS (ESI): Calcd. for $C_{18}H_{20}NO_5$ (MH^+): 330.1341. Found: 330.1330.

Ethyl 2-(phenylmethyl)-3-hydroxy-3-(4-nitrophenyl)propanoate 12b (Procedure A). [147 mg, 68% yield from **3a** (100 mg)]. R_f 0.28 (Cyclohexane/AcOEt = 80:20). Colorless oil. ***First diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$)·δ 0.94 (t, 3 H, $^3J_{HH}$ = 6.8 Hz, CH_3), 2.81-2.86 (m, 1 H, CHBn), 2.97-3.02 (m, 2 H, CH_2Ph), 3.44 (br.s, 1 H, OH), 3.89-3.96 [m, 2 H, CH_2(Et)], 5.16 [d, 1 H, $^3J_{HH}$ = 3.8 Hz, CH(OH)], 7.04 (d, 2 H, $^3J_{HH}$ = 8.7 Hz, H_{Ar}), 7.13-7.25 (m, 3 H, H_{Ar}), 7.58 (d, 2 H, $^3J_{HH}$ = 8.7 Hz, H_{Ar}), 8.20 (d, 2 H, $^3J_{HH}$ = 8.7 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 32.8 (CH_2Ph), 54.4 (CHBn), 60.9 [CH_2(Et)], 72.9 (CHOH), 123.6, 126.5, 127.1, 128.4, 128.8, 138.3, 147.5, 148.6 (C_{Ar}), 174.2 (C=O). IR (neat) 3481 (O-H); 1722 (C=O); 1603; 1519; 1344 cm^{-1}. ***Second diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.84-3.00 (m, 3 H, CHBn), 3.68 (d, 1 H, $^3J_{HH}$ = 8.0 Hz, OH), 3.82-3.95 [m, 2 H, CH_2(Et)], 4.79 [dd, 1 H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 4.3 Hz, CH(OH)], 7.11-7.24 (m, 5 H, H_{Ar}), 7.41 (d, 2 H, $^3J_{HH}$ = 8.5 Hz, H_{Ar}), 8.11 (d, 2 H, $^3J_{HH}$ = 8.5 Hz, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 35.8 (CH_2Ph), 53.9 (CHBn), 61.0 [CH_2(Et)], 72.9 (CHOH), 123.6, 126.8, 126.9, 128.6, 129.0, 137.7, 147.4, 149.7 (C_{Ar}), 174.2 (C=O). IR (neat) 3531 (O-H), 1732 (C=O), 1604, 1516, 1351 cm^{-1}. HRMS (ESI): Calcd. for $C_{18}H_{20}NO_5$ (MH^+): 330.1341. Found: 330.1330.

Ethyl 2-[hydroxy(4-nitrophenyl)methyl]-4-oxo-4-phenylbutanoate 12c (Procedure A). [55 mg, 77% yield from **3b** (50 mg)]. R_f 0.2 (Cyclohexane/AcOEt = 70:30). Colorless oil. ***Major diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.20-3.43 (m, 3 H), 3.77 (d, 1 H, $^3J_{HH}$ = 6.2 Hz, OH), 3.98-4.06 [m, 2 H, CH_2(Et)], 5.09 [t, 1 H, $^3J_{HH}$ = 6.2 Hz, CH(OH)], 7.25-7.56 (m, 5 H, H_{Ar}), 7.84 (d, 2 H, $^3J_{HH}$ = 8.4 Hz, H_{Ar}), 8.12 (d, 2 H, $^3J_{HH}$ = 8.4 Hz, H_{Ar}),. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 37.4 (CH_2), 47.3 (CH), 61.4 [CH_2(Et)], 73.0 (CH), 123.6, 127.0, 128.1, 128.7, 133.7, 136.2, 147.5, 149.0, 173.6 (C=O), 197.4 (C=O). ***Minor diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.97 [$\delta_{A(ABX)}$, 1 H, J_{AB} = 20.8, J_{AX} = 7.2 Hz, $CH_2(H_a)$], 3.17-3.43 (m, 3 H), 4.06-4.15 [m, 2 H, CH_2(Et)], 5.31 [br.s, 1 H, CH(OH)], 7.25-7.56 (m, 5 H, H_{Ar}), 7.79 (d, 2 H, $^3J_{HH}$ = 8.4 Hz, H_{Ar}), 8.12 (d, 2 H, $^3J_{HH}$ = 8.4 Hz, H_{Ar}),. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 34.7 (CH_2), 47.8 (CH), 61.4 [CH_2(Et)], 72.6 (CH), 123.7, 126.9, 128.0, 128.6, 133.5, 136.3, 147.4, 148.6, 173.2 (C=O), 198.1 (C=O). IR (neat) 3475 (O-H), 1725 (C=O), 1683 (C=O), 1517, 1343 cm^{-1}. HRMS (ESI): Calcd. for $C_{19}H_{19}NO_6$ (MH^+): 358.1291. Found: 358.1293.

Ethyl 2-phenyl-2-methyl-3-hydroxy-3-(4-nitrophenyl) propanoate 12d (Procedure E or Procedure C). Purification on silica-gel column chromatography (cyclohexane/Et_2O = 90:10). [54 mg, 39% yield from **3a** (100 mg). Two diastereoisomers. Colorless oil. ***First diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.44 (s, 3 H, CH_3), 3.70 (d, 1 H, $^3J_{HH}$ = 2.6 Hz, OH), 4.14 (ABX_3, 2 H, CH_2O), 5.30 [d, 1 H, $^3J_{HH}$ = 2.6 Hz, CH(OH)], 6.80-7.23 (m, 7 H, H_{Ar}), 7.97 (d, 2 H, $^3J_{HH}$ = 8.8 Hz, H_{Ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.2 (CH_3), 55.5 (CH), 61.7 (ArCH), 77.9, 122.4, 127.8, 128.0, 129.2, 137.0, 146.2, 147.4 (C_{Ar}), 176.5 (C=O). ***Second diastereomer:*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.42 (s, 3 H, CH_3), 3.91 (d, 1 H, $^3J_{HH}$ = 3.0 Hz, OH), 4.14 (ABX_3, 2 H, CH_2O), 5.43 [d, 1 H, $^3J_{HH}$ = 3.0 Hz, CH(OH)], 6.78-7.23 (m, 7 H, H_{Ar}), 7.83 (d, 2 H, $^3J_{HH}$ = 8.8 Hz, H_{Ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1 (CH_3), 19.2 (CH_3), 56.3 (CH), 61.8 (ArCH), 77.9, 122.1, 126.6, 127.9 (CH_{ar}), 128.4, 128.7, 139.0, 145.9, 147.1 (C_{Ar}), 177.1 (C=O). HRMS (ESI) Calcd for $C_{18}H_{20}NO_5$ (MH^+): 330.1341, Found: 313.1330.

2-(*N*-acetylamino)-2-carboethoxy-3-(phenylmethyl)propionic acid 11e[48]. [1.7 g, 89% yield from malonate (2 g)]. White solid (mp 135 °C). ^{1}H NMR ($CDCl_3$) δ 1.24 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 1.92 [s, 3 H, CH_3], 3.39 [$\delta_{A(AB)}$, 1 H, J_{AB} = 13.6 Hz, CH_2], 3.45 [$\delta_{B(AB)}$, 1 H, J_{AB} = 13.6 Hz, CH_2], 4.12 [q, 2 H, J = 7.2 Hz, CH_2(Et)], 6.99-7.29 (m, 5 H, H_{Ar}), 13.74 (bs, 1 H, CO_2H). ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 37.3, 61.3, 66.8, 126.7, 128.1, 129.8, 135.6, 167.5, 168.3, 169.2. IR (neat) 3324 (O-H), 1721 (C=O), 1598, 1525, 1201 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{17}NO_5$ (MH^+): 280.1172, Found: 280.1185.

Ethyl 2-(*N*-acetylamino) -2-(phenylmethyl) -3-hydroxy-3-(4-nitrophenyl) propanoate 12e (Procedure C). [144 mg, 77% yield from **11e** (134 mg)]. ***First diastereomer:*** Light brown solid (mp 125 °C). R_f 0.25 (Cyclohexane/AcOEt = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 1.98 (s, 3 H, $COCH_3$), 3.05-3.10 (m, 2 H, CH_2Ph), 4.05-4.21 [m, 2 H, CH_2(Et)], 5.60 (s, 1 H, CHOH), 5.85 (bs, 1 H, OH), 5.99 (s, 1 H, NH), 7.02 (m, 2 H, H_{Ar}), 7.26 (m, 2 H, H_{Ar}), 7.48 (d, 2 H, J = 6.8 Hz, H_{Ar}), 8.19 (d, 2 H, J = 6.8 Hz, H_{Ar}), 8.26-8.33 (m, 1 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 [CH_3(Et)], 24.1 ($COCH_3$), 37.6 (CH_2Ph), 62.8 [CH_2(Et)], 70.7, 77.0 (COH), 123.3, 127.6, 128.1, 128.8, 129.7, 131.3, 134.7, 147.4, 170.4, 172.3 (C=O). IR (neat) 3260 (OH), 1728, 1645 (C=O), 1510, 1345 cm^{-1}. HRMS (ESI) Calcd for $C_{20}H_{23}N_2O_6$ (MH^+): 387.1556, found: 378.1567. ***Second diastereomer:*** Light brown solid (mp 123 °C). R_f 0.1 (Cyclohexane/AcOEt = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 [t, 3 H, J = 7.2 Hz, CH_3(Et)], 1.98 (s, 3 H, $COCH_3$), 3.46 [d, 1 H, J = 14.0 Hz, CH_2Ph (H_a)], 4.07 [d, 1 H, J = 14.0 Hz, CH_2Ph (H_b)], 4.23-4.32

[m, 2 H, CH_2(Et)], 5.47 [d, 1 H, J = 10.4 Hz, CHOH], 6.36 (s, 1 H, NH), 7.02 (m, 2 H, H_{Ar}), 7.25-7.33 (m, 5 H, H_{Ar}), 8.14 [d, 2 H, J = 6.8 Hz, H_{Ar}]. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 [CH_3(Et)], 23.6 ($COCH_3$), 38.0 (CH_2Ph), 63.3 [CH_2(Et)], 72.2, 77.9 (COH), 123.4, 126.9, 127.5, 128.6, 129.6, 135.2, 147.5, 148.2, 170.6, 172.9 (C=O). IR (neat) 3286 (OH), 1713, 1641 (C=O), 1519, 1347 cm^{-1}. HRMS (ESI) Calcd for $C_{20}H_{23}N_2O_6$ (MH^+): 387.1556, found: 378.1563.

Acknowledgements

We gratefully acknowledge Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship to PL, ANR "Mesorcat", CNRS and its program "Chimie pour le Dévelopement Durable", Région Basse-Normandie, and the European Union (FEDER funding) for financial supports.

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