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Asymmetric Malonic and Acetoacetic Acid Syntheses – A Century of Enantioselective Decarboxylative Protonations

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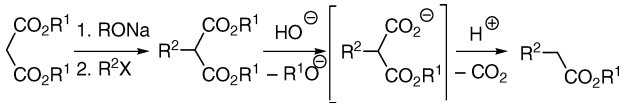
The enantioselective decarboxylative protonation (EDP) of malonic or acetoacetic acid derivatives is a synthetic methodology by which the chirality of the product is generated during the enol/enolate protonation step. Although EDP is a century-old reaction, it has not received much attention until recently. This review focuses on the EDP as an alternative to the strong-base-mediated deprotonation/asymmetric reprotonation for the stereocontrol of C–H bond formation. The diverse synthetic approaches are classified according to the type of catalysis used, which are organic, metallic or enzymatic.

Introduction

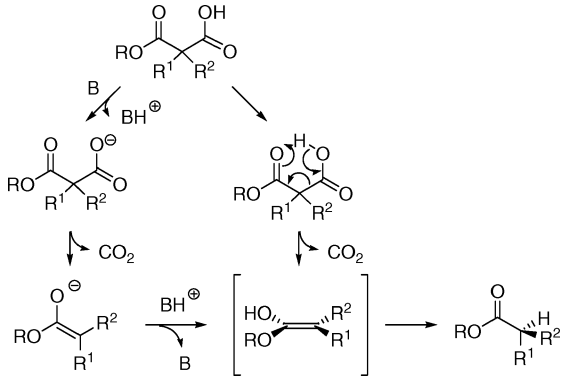
The malonic acid synthesis is an old yet useful method for the synthesis of α-substituted and α,α-disubstituted carboxylic acids and their derivatives. Related to this reaction is the acetoacetic acid synthesis allowing the synthesis of substituted ketones. Both syntheses rely on sequential alkylations with weak bases under mild conditions followed by ester hydrolysis or saponification and decarboxylation (Scheme 1).



Scheme 1.

It has been generally accepted that the mechanism for the loss of CO_2 from β-oxo acids involves a unimolecular decomposition that proceeds through a cyclic proton transfer (Scheme 2).[1,2]

Starting from a chiral or prochiral compound, the asymmetry of the carbon atom bearing the carbonyl groups vanishes at the enol stage to reappear during the tautomerization, which represents a carbon protonation "stereoablative reaction".[3] The chirality is thus determined at the last stage of the reaction and is induced by an optically active source not covalently linked to the substrate but intimately involved in both the C–C bond-breaking and enantioselective C–H bond formation. The whole process is thus related to the enantioselective protonations of achiral enolates.



Scheme 2.

The following review concentrates on EDP and describes a century of efforts to achieve the highest selectivities mediated by three main types of chiral inductors: organic bases, organometallic complexes and biocatalysts (isolated enzymes or microorganisms). The diastereoselective decarboxylative protonation is beyond the scope of this review.

The First EDP – A Historical Perspective

Thermal Decarboxylation of Prochiral Substrates

The first asymmetric decarboxylation, which was also the first asymmetric reaction in the literature, was described in 1904 by Marckwald.[4] Ethyl(methyl)malonic

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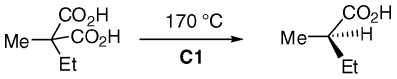
acid (**1**) heated at 170 °C with brucine (**C1**) yielded 2-methylbutanoic acid (**2**) in 10% enantiomeric excess (*ee*) (Scheme 3, Figure 1).



1 **2** *ee* 10 %

Scheme 3.

Several decades later, Kenyon et al.[5] failed to reproduce these results. Verbit et al.[6] reported the formation of (*R*)-2-phenylbutanoic acid (**4**) with 18% *ee* when ethyl(phenyl)-malonic acid (**3**) (Scheme 4) was heated in cholesteryl benzoate (**C2**) at 160 °C for 2 h, a liquid crystal that possesses molecular chirality and macrochirality owing to the helical arrangement of the mesophase. This asymmetric induction was revisited by Kagan et al., but all experiments afforded racemic 2-phenylbutanoic acid (**4**).[7]

Copper Complexes

Maumy et al. described the first mild method for the decarboxylation of prochiral alkyl(phenyl)malonic acids **5**.[8] With a combination of copper(I) chloride and cinchonidine (**C3**) in acetonitrile at 60 °C, methyl(phenyl)- and isopro-

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Jérôme Baudoux earned his PhD in 2004 from the University of Rouen under the supervision of Dr. Jean-Christophe Plaquevent and Dr. Dominique Cahard. He undertook postdoctoral studies at the University of Nottingham with Professor Nigel S. Simpkins. He then held a temporary position as a teaching and research assistant at the University of Caen, where he worked with Professor Pierre-Jean Madec. In 2006, he took a position as an assistant professor in the same university working with Professors Jacques Rouden and Marie-Claire Lasne.

Mukkanti Amere was born in Panchalavaram (India) and earned a PhD in 2004 from the University of Hyderabad (India). After a brief stint as research associate at the University of Hyderabad, he moved to LCMT (France) as a CNRS postdoctoral fellow to work on asymmetric organocatalysis from 2005 to 2007. Recently, he took an industrial research position at Organix Inc. (USA) and is currently engaged in NIH projects to synthesize cannabinoid analogs.

Professor Marie-Claire Lasne received her PhD from the University of Caen (France) in 1974. She undertook postdoctoral studies with Professor Jerrold Meinwald at Cornell University in 1975. Since 1969, she has worked as a lecturer, then as a Professor at the University of Caen. In 1987, she spent a sabbatical year in Hammersmith Hospital, MRC Cyclotron Unit (London, UK) in V. Pike's group. Her research interests include the synthesis of reactive unsaturated molecules with flash vacuum pyrolysis, cross-coupling reactions, the synthesis and radiosynthesis with positron emitters (^{11}C and ^{18}F) of molecules for in-vivo imaging, asymmetric protonations and organocatalysis.

Jacques Rouden received his Ph.D. from the University Paris XI at Orsay (France) in 1990 under the guidance of Professor H.-P. Husson and Dr. J. Royer. After postdoctoral studies in the USA and Canada between 1991 and 1997, he joined the University of Caen as an assistant professor working with Professor Lasne on radiolabelling chemistry with positron emitters (PET Chemistry). He was promoted to Professor at ENSICAEN in 2005. His research interests include the use of transition-metal complexes and the development of organocatalysed reactions in organic synthesis.

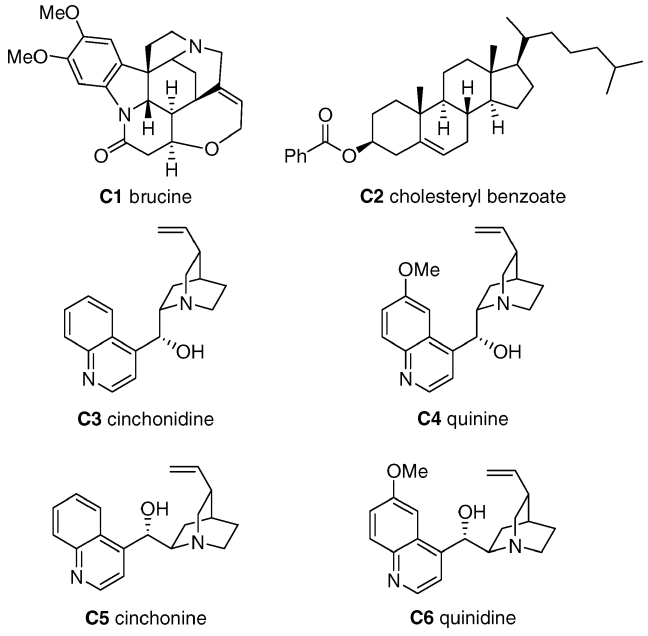
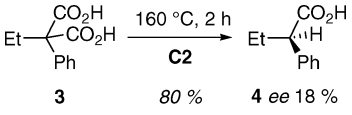
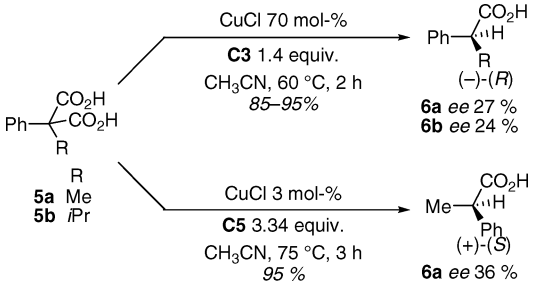


Figure 1. Chiral sources **C**.



Scheme 4.

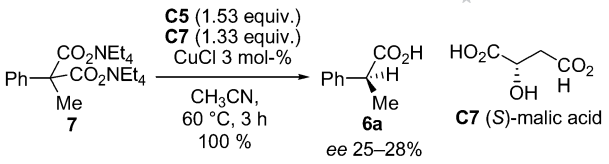
pyl(phenyl)acetic acids (**6a**,**b**) were obtained in 27 and 24% *ee*, respectively (Scheme 5). The acidic character of the substrates required at least 1 equiv. of a chiral base.



Scheme 5.

Brunner et al. showed that the amount of copper(I) chloride could be reduced to 3 mol-% for the decarboxylation of malonic acid **5a**, but a large excess of cinchonine (**C5**) was used (Scheme 5). Under such conditions, the enantioselectivity reached 36% *ee*.[9]

Similarly, the tetraethylammonium salt **7** was decarboxylated with CuCl (3 mol-%), cinchonine (**C5**) and a chiral carboxylic acid (Scheme 6). The highest selectivity was obtained with (*S*)-malic acid (**C7**) (25–28% *ee*, Scheme 6).[9]



Scheme 6.

The role of copper in the decarboxylation of malonic acids and esters was extensively studied.[10] The decarboxylation of alkyl(phenyl)malonic acid derivatives occurred by a predissociation step involving metal–carboxylate bond cleavage, thus minimizing the effect of copper on the carbon dioxide extrusion. Consistent with this mechanistic proposal, the rates of decarboxylation were greatly enhanced upon sequestering the metal cation with a chelating nitrogen base. In a survey of the reaction conditions, Brunner's group[11] observed that the decarboxylation of phenyl- and methyl(phenyl)malonic acids with Cu_2O was far more effective than that with CuCl, suggesting that a higher basicity of the anion favours the decarboxylation. Moreover, since the rate constants of the decarboxylation of the hydrogen phenylmalonate salts **8** and **9** (Figure 2) were nearly identical, it was deduced that the monoanions of malonic derivatives were the reactive species undergoing decarboxylation. Shortly thereafter, Muzart et al.[12] reached the same conclusion, that is that copper is not necessary to catalyse the decarboxylation.

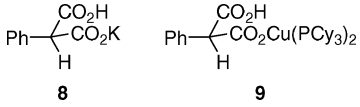
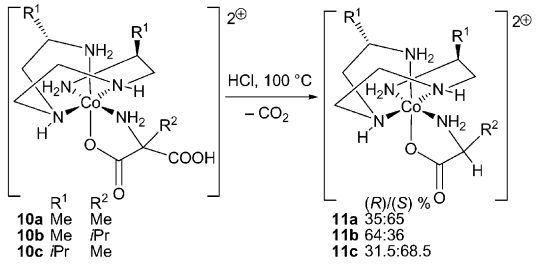


Figure 2. Phenylmalonate salts.

(Amino acid)cobalt(III) Complexes

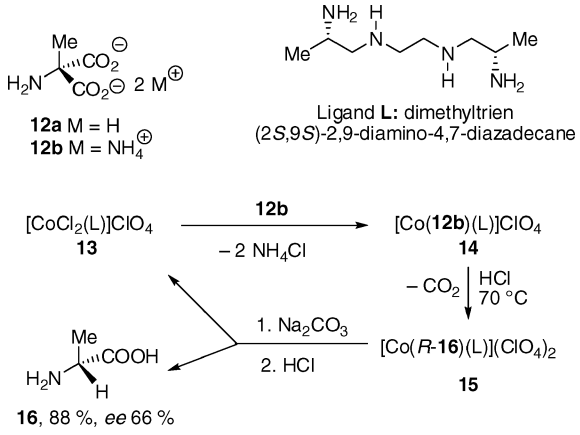
The stereoselective decarboxylation of α-amino-α-methylmalonic acid coordinated to the [(2*S*,9*S*)-2,9-diamino-4,7-diazadecane]cobalt complex was first reported in 1967.[13] It yielded (*S*)-alanine in 14% *ee*. This result was not reproducible, and it was later shown that complexes **10a** underwent enantioselective decarboxylation upon warming in acidic solution, leading to complexes (*S*)-**11a** and (*R*)-**11a** in 65 and 35% yield, respectively (Scheme 7).[14] The effects



Scheme 7.

of bulkier substituents indicated that the bulkiness of R^2 on the malonate moiety was more important than that of R^1 on the tetraamine ligand.

The mild decarboxylative conditions (Na_2CO_3, 50 °C, 30 min) of cobalt/tetra-amine/alkyl(amino)malonate[15] allowed for the isolation of the amino acids with retention of configuration at the asymmetric carbon centre while also preserving the complexes (Scheme 8). The decarboxylation of amino(methyl)malonate complex **14**, formed from the cobalt complex of dimethyltrien (L) and ammonium methylmalonate (**12b**), produced predominantly an (*R*)-alaninato complex **15**, from which alanine **16** [66% *ee* for (2,4-dinitrophenyl)alanine] and the complex were easily released upon acidic workup.



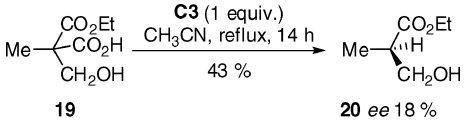
Scheme 8.

Enantioselective Decarboxylative Protonation Mediated by a Chiral Base

Alkyl(aryl)hemimalonic Esters

The first EDPs carried out by Maumy et al.[8b] and later by Brunner et al.[9] with racemic malonic substrates were performed with cinchona alkaloids and copper chloride (Scheme 5). This additive was shown later to be useless in the EDP reaction (Table 1, Entries 1–6).[10,11] For example, Brunner observed a higher induction in the decarboxylation of monoester **17a** (36% *ee*) by using an excess of base with a catalytic amount of copper (Table 1, compare Entries 5 and 6). The same reaction conducted in THF with only 10 mol-% of cinchonine (**C5**) in the absence of copper(I) at room temperature afforded **18a** in 34% *ee* (Table 1, Entry 7). The stereoselectivity was similar to that obtained when the copper salt was used (the thermal stability of the substrate without base at room temperature was noteworthy), demonstrating the catalytic role of the alkaloid in the decarboxylation process.

Enantioselective decarboxylation catalysed by cinchona alkaloids was envisaged to provide a ready access to β-hydroxyisobutyric acids. Under the best conditions [in acetonitrile, with a stoichiometric amount of cinchonidine (**C3**)], β-hydroxyisobutyric ester **20** was obtained in low enantioselectivity and moderate yield (Scheme 9).[16] No enantioselectivity was observed with 10 mol-% of base.

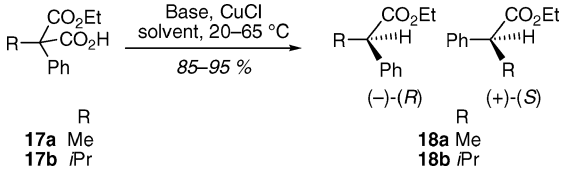


Scheme 9.

β-Oxo Acids

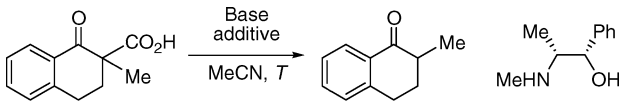
Another proof of the uselessness of copper derivatives in the EDP was demonstrated in the decarboxylation of β-oxo acid **21** (Table 2, compare Entries 1–3 and 7 with Entries 4–6).[12] With ephedrine (**C8**) as the catalyst, 2-methyl-1-tetralone (**22**) was obtained with 30–35% *ee*. The (*S*) product was obtained as the major enantiomer, whereas the (*R*) enantiomer was formed with cinchonine (**C5**, Table 2, Entry 8).

Table 1. Maumy's and Brunner's EDP of malonic acid hemiesters.



Entry	Base [equiv.]	*T* [°C]	Solvent	CuCl [equiv.]	Product	*ee* [%] (config.)
1	**C3** (0.4)	60	MeCN	0.2	**18a**	17 (*R*)[8b]
2	**C3** acetate (0.4)	60	MeCN	0.2	**18a**	15 (*S*)[8b]
3	**C1** (0.4)	60	MeCN	0.2	**18a**	7 (*R*)[8b]
4	**C3** (0.4)	60	MeCN	0.2	**18b**	31 (*R*)[8b]
5	**C5** (0.4)	65	MeCN	0.03	**18a**	19 (*S*)[9]
6	**C5** (3.3)	85	MeCN	0.03	**18a**	36 (*S*)[9]
7	**C5** (0.1)	room temp.	THF	0	**18a**	34 (*S*)[11]
8	**C3** (0.1)	room temp.	THF	0	**18a**	16 (*R*)[11]
9	**C4** (0.1)	room temp.	THF	0	**18a**	12 (*R*)[11]
10	**C6** (0.1)	room temp.	THF	0	**18a**	14 (*S*)[11]

Table 2. EDP of β-oxo acid **21** to tetralone **22**.[12]



21 **22** **C8**

Entry	Base (equiv.)	Additive (equiv.)[a]	*T* [°C]	*t* [h]	*ee* [%] (config.)
1	**C8** (0.55)	hν	0	0.45	20
2	**C8** (1.1)	hν	0	0.45	30
3	**C3** (1.1)	hν	0	0.45	30
4	**C8** (0.55)	Cu_2O (2)	room temp.	18	17
5	**C8** (0.5)	Cu_2O (0.2)	room temp.	18	5
6	**C8** (0.4)	CuCl (0.2)	room temp.	18	8
7	**C8** (0.2)	–	room temp.	22	35 (*S*)
8	**C5** (0.2)	–	room temp.	22	35 (*R*)

[a] Irradiation was performed at 337 nm.

2-Cyanopropionic Acid Derivatives

The first efficient EDP catalysed by an organic base was developed for the synthesis of a direct precursor of (*S*)-naproxen, an anti-inflammatory agent (Figure 3, Table 3).[17] As cinchona alkaloids appeared to be the most efficient catalysts, around thirty analogues were synthesized and tested. Some of these are represented in Figure 4.

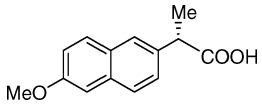
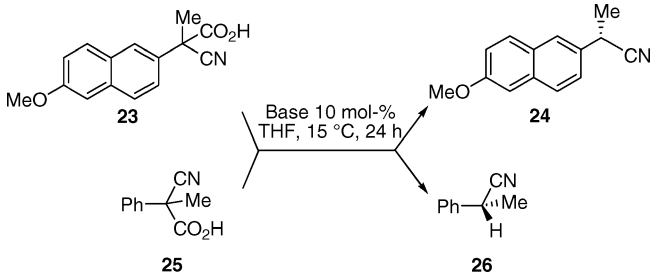


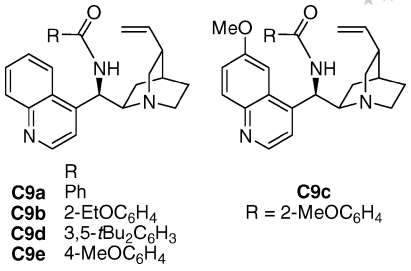
Figure 3. (*S*)-Naproxen.

Table 3. EDP of 2-cyanopropionic acid derivatives.[17]



Entry	Base	*ee* [%]	Product[a]	Config.
1	**C3**	6	**24**	(*R*)
2	**C4**	13	**24**	(*R*)
3	**C5**	17	**24**	(*S*)
4	**C6**	34	**24**	(*S*)
5	**C9a**	51	**24**	(*S*)
6	**C9b**	72	**24**	(*S*)
7	**C5**	13	**26**	(*S*)
8	**C9b**	60	**26**	(*S*)

[a] 100% conversion.



R
C9a Ph
C9b 2-$EtOC_6H_4$
C9d 3,5-$tBu_2C_6H_3$
C9e 4-$MeOC_6H_4$

C9c
R = 2-$MeOC_6H_4$

Figure 4. Some of the most efficient alkaloid derivatives tested in the EDP of 2-cyanopropionic acid derivatives and aminohemimalonates.

A comparison of the data obtained with common alkaloids **C3**–**C6** is presented in Table 3 (Entries 1–6). The highest selectivity (72% *ee*) was reached with cinchonine 9-*epi*-benzamide derivative **C9b** (10 mol-%) in anhydrous THF at 15 °C for 24 h.

Catalytic and stoichiometric amounts of catalyst afforded similar asymmetric inductions, and THF was the optimal solvent. A kinetic study showed that the enantioselectivity did not change with time, and a plot of conversion vs. time was linear, indicating zero-order behaviour of acid **23**. A comparative study of the EDP of 2-cyano-2-phenylpropionic acid (**25**) was carried out (Table 3, Entries 7–8). Nitrile **26** was obtained in slightly lower enantioselectivity than that of the naproxen precursor **24**.[17]

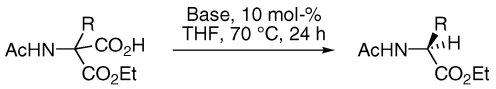
A DFT computational study of the stereoselective decarboxylation of nitrile **23** was reported.[18] According to quantum-chemical gas-phase calculations, CH···O and N–H···O interactions between the chiral base and the substrate in the transition state stabilize the (*S*) enantiomer by 3.7 kcal mol^{-1}. The calculated energy profile for the proposed sequence of deprotonation of the acid, decarboxylation and reprotonation of the intermediate ketenimine anion was several kcal mol^{-1} less favourable than that of the concerted reaction, which required a gas-phase activation enthalpy of 21.2 kcal mol^{-1}. The transition state did not involve a planar prochiral intermediate, as proposed initially.

Aminohemimalonates

The synthesis of proteinogenic and non-proteinogenic amino acids, continues to be a challenge, although many synthetic approaches are available. Brunner et al.[19] reported a methodology similar to that developed for naproxen precursor **24** to obtain acyclic enantioenriched amino acid derivatives from 2-aminomalonates. 2-(Acetylamino)-2-alkylmalonic hemiesters **27** were subjected to the action of 10 mol-% of a cinchona-based catalyst in THF at 70 °C for 24 h. Selected results are presented in Table 4.

Full conversion and the highest selectivity (71% *ee*) was achieved with the epicinchonine benzamide derivative **C9e** with 2-amino-2-benzylmalonate **27c** as the substrate (Table 4, Entry 6). Valine and alanine acetamides **28a** and **28b** were produced with slightly lower enantioselectivities (Table 4, Entries 2 and 4) with catalyst **C9d**. An increase in

Table 4. EDP of acyclic amino hemimalonates **27a**–**c**.[19]



27a Me **27b** *i*Pr **27c** Bn — **28a** Me **28b** *i*Pr **28c** Bn

Entry	Base	Product[a]	*ee* [%] (config.)
1	**C9b**	**28a**	19 (*S*)
2	**C9d**	**28a**	60 (*S*)
3	**C9d**[b]	**28a**	63 (*S*)
4	**C9d**	**28b**	48 (*S*)
5	**C9a**	**28c**	69 (*S*)
6	**C9e**	**28c**	71 (*S*)

[a] 100% conversion. [b] 30 mol-% of base was used.

catalyst loading to 30 mol-% slightly improved the enantioselectivity of **24a** (Table 4, Entry 3). Comparatively, natural cinchona alkaloids afforded poor selectivities with such substrates (<10% *ee*, data not shown).

A kinetic study of the decarboxylation of hemimalonate **27a** with catalyst **C9d** showed a small increase in the selectivity during the first part of the reaction (5 h) but then remained constant until full conversion was reached after 12 h. No kinetic resolution was observed as in the naproxen system. Interestingly, both enantiomers of 2-cyanopropionic derivative **23** were obtained with similar but opposite enantioselectivities (Figure 5). Such a result ruled out a concerted mechanism (as proposed previously, see ref.[18]) and favoured the mechanism involving a stereoselective protonation of a planar enolate (Scheme 2).

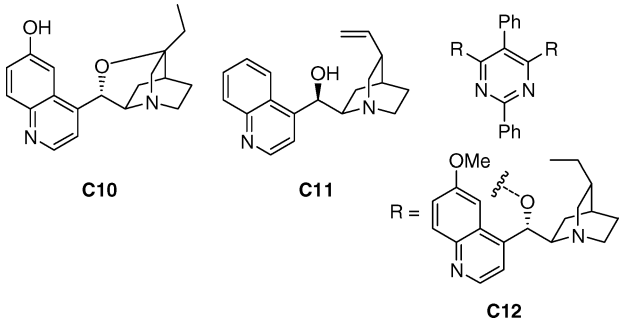
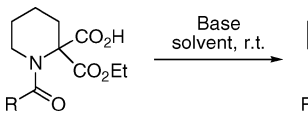


Figure 5. Alkaloids tested in the EDP of aminomalonates.

En route to the synthesis of a pipecolic acid derivative as a precursor of a potent muscarinic receptor antagonist,[20] the EDP of hemimalonic ester **29a** was envisaged.[21]

Several bases including cinchona alkaloids were tested. According to Brunner's conditions, with 1 equiv. of catalyst **C9c** or isocupreidine (**C10**), *N*-acetylpipecolate **30a** was isolated in 52% and 37% *ee*, respectively, and in good yields (Table 5, Entries 1 and 2). The use of a catalytic amount of **C10** led to lower enantioselectivity (Table 5, Entry 3), a trend not observed with the bis(alkaloid) **C12** (Table 5, Entries 4 and 5).

Table 5. Decarboxylation of pipecolates **29a**–**e**.[a]



29 — (*S*)-**30**

30a Me **30b** Ph **30c** 4-$MeOC_6H_4$ **30d** 4-$O_2NC_6H_4$ **30e** 1-naphthyl

Entry	Solvent	Base (equiv.)	Product	*ee* [%]	Config.
1	THF	**C9c** (1)	**30a**	52	(*S*)[21]
2	THF	**C10** (1)	**30a**	37	(*S*)[21]
3	THF	**C10** (0.1)	**30a**	18	(*S*)[21]
4	THF	**C12** (1)	**30a**	24	(*S*)[21]
5	THF	**C12** (0.1)	**30a**	25	(*S*)[21]
6	THF	**C5** (1)	**30a**	6	(*R*)[21]
7	THF	**C5** (1)	**30b**	33	(*R*)[22]
8	toluene	**C5** (1)	**30b**	61	(*R*)[22]
9	CCl_4	**C5** (1)	**30b**	63	(*R*)[22]
10	THF	**C11** (1)	**30b**	66	(*R*)[22]
11	CCl_4	**C11** (1)	**30b**	72	(*R*)[22]
12	CCl_4	**C11** (0.1)	**30b**	71	(*R*)[b][22]
13	CCl_4	**C11** (1)	**30c**	67	(*R*)[22]
14	CCl_4	**C9c** (1)	**30d**	67	(*R*)[22]
15	CCl_4	**C5** (1)	**30e**	59	(*R*)[22]

[a] Reaction conditions: room temp., 16–72 h. [b] Carried out on a 10 mmol scale.

Improved results[22] were obtained with 9-*epi*-cinchonine (**C11**) as the base and *N*-benzoylpiperidinyl derivative **29b** as the substrate (Figure 5). Solvents of low polarity such as carbon tetrachloride and toluene and an *N*-benzoyl protecting group on the substrate (Table 5, comparison of Entries 6–9) were beneficial in these EDPs. Among the catalysts tested, cinchonine proved superior, and the 9-*epi*-configured catalysts afforded better enantioselectivities (Table 5, compare Entries 9 and 11) than did quinidine analogues (data not shown). The temperature influenced only the rate of the decarboxylation, not the selectivity. The reaction was tested successfully on a multigram scale with a catalytic amount of *epi*-cinchonine **C11** without loss of selectivity (Table 5, Entry 12).

Because of their intrinsic properties (the strong H-bonding ability of the thiourea and amino groups facilitate its action as a chiral proton shuttle), 9-*epi*-quinidine–thiourea **C13a** and its pseudoenantiomer **C13b**, derived from quinine, were tested in the EDP of cyclic and acyclic hemimalonic esters **29a**–**b**, **27b**–**c** and **31** (Figure 6 and Scheme 10).[23] Selected results are presented in Table 6.

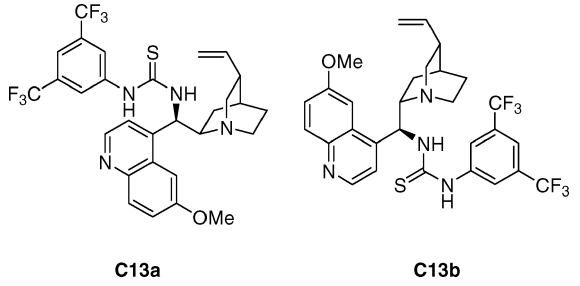
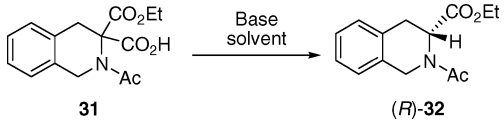


Figure 6. Thioureas derived from cinchona alkaloids.



Scheme 10.

Table 6. Decarboxylative protonation mediated by thioureas **C13a**,**b**.[a]

Entry	Solvent	Base	Product	*ee* [%]	Config.
1	acetone	**C13b**	**30b**	89	(*R*)[23]
2	acetone	**C13a**	**30a**	93	(*S*)[23]
3	acetone	**C13b**	**30a**	89	(*R*)[23]
4	MeCN	**C13a**	**28c**	82	(*S*)[23]
5	THF	**C13a**	**28b**	89	(*S*)[23]
6	acetone	**C13b**	**28b**	88	(*R*)[23]
7	acetone	**C13b**	**32**	88	(*R*)[23]

[a] Reaction conditions: base (1 equiv.), 0 °C, 7 d.

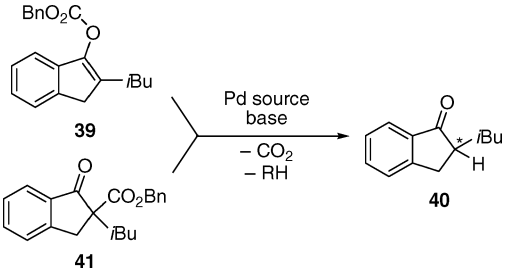
The thiourea alkaloid derivatives **C13a** and **C13b** afforded the highest enantioselectivity achieved so far for decarboxylative protonation mediated by a chiral base. Both enantiomers of products **28** (Table 6, Entries 5 and 6), **30** (Table 6, Entries 2 and 3) and the isoquinoline derivative **32** (Table 6, Entry 7 and Scheme 10) can be prepared with similar selectivities with thiourea **C13a** or its pseudoenantiomer **C13b**. Although a stoichiometric amount of base is required, its ready access and easy recovery, the broad range of solvents it can be used with and the mild conditions required make this methodology attractive for the synthesis of α-amino esters and a valuable alternative to the asymmetric protonation of lithium enolates.

Metal-Catalysed EDP

Pd-Catalyzed Deprotection and EDP of Prochiral Cyclic Allyl or Benzyl Enol Carbonates

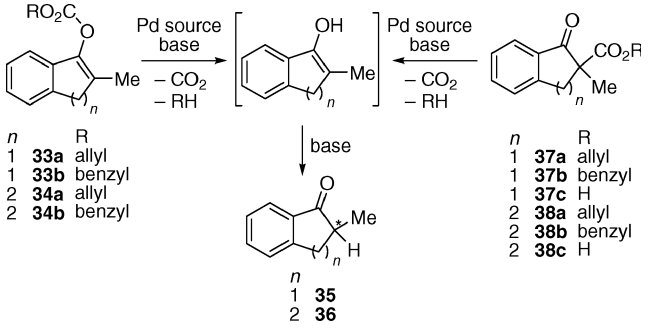
The Pd-catalyzed deprotection/decarboxylation of allyl- or benzyl-carboxylated compounds has been widely used in organic synthesis. Two types of substrates, enol carbonates and β-oxo esters, were used to lead to enols as transient species. In the presence of a chiral proton source (Figure 7), the asymmetric protonation of the enol was expected to give an enantioenriched ketone (Scheme 11).[24] The first studies by Muzart et al.[25–28] were carried out with carbonates **33a** and **33b**. Ketone **35** was obtained in high yield and moderate selectivity with ephedrine (**C8**) and amino alcohol **C14** (Table 7, Entries 1 and 3). A survey of different chiral proton sources showed that it was necessary to use an amino alcohol rather than an alcohol, an amine or an acid as the chiral catalyst. For the deprotection of carbonate **33a**, 1 equiv. of amino alcohol was required as an allyl group scavenger. This was confirmed by the isolation of *N*-allylephedrine in 95% yield.[25] Under similar conditions, 2-methyltetralone **36** was prepared (86–90% yields) from carbonates **34a** and **34b** in 50 and 77% *ee*, respectively, with ephedrine (**C8**) and the amino alcohol **C14** (Table 7, Entries 6 and 10).

Figure 7. Selected chiral amino alcohols used in the Pd-catalyzed deprotection and EDP.



Scheme 11.

Table 7. Pd-catalyzed deprotection of prochiral enol carbonates and EDP.



Entry	Substrate	Base (equiv.)	Conditions	Product, *ee* [%] (config.)
1	**33a**	**C8** (1.56)	0 °C, 24 h[a]	**35**, 38 (*R*)[25]
2	**33b**	**C15** (0.34)	room temp., 1 h[b]	**35**, 30 (*R*)[25]
3	**33b**	**C14** (0.30)	room temp., 1.5 h[b]	**35**, 40 (*R*)[25]
4	**33b**	**C16a** (0.3)	50 °C, 20 min[b]	**35**, 60 (*R*)[26]
5	**33b**	**C14** (0.3)	45 °C, 20 min[b]	**35**, 64 (*R*)[27]
6	**34a**	**C8** (2)	room temp., 4 h[c]	**36**, 50 (*R*)[28]
7	**34b**	**C8** (0.3)	room temp., 1 h[b]	**36**, 26 (*R*)[28]
8	**34b**	**C16a** (0.3)	70 °C, 14 min[b]	**36**, 56 (*R*)[26]
9	**34b**	**C17** (0.3)	room temp., 2.5 h[b]	**36**, 63 (*R*)[28]
10	**34b**	**C14** (0.3)	70 °C, 24 min[b]	**36**, 77 (*R*)[27]
11	**39**	**C14** (0.3)	55 °C, 25 min[b]	**40**, 66 (*R*)[27]

[a] Reaction conditions: $Pd(OAc)_2$ (6 mol-%), PPh_3 (12 mol-%), MeCN. [b] Reaction conditions: Pd/C (2.5 mol-%), H_2, MeCN. [c] Reaction conditions: $Pd(OAc)_2$ (5 mol-%), PPh_3 (10 mol-%), toluene.

The bicyclic chiral sources **C14**, **C16a** and **C17** were more efficient than ephedrine (**C8**) (Table 7, Entries 7–10) in the EDP of carbonate **34b**. Substitution of the methyl group of **33b** by an *i*Bu group decreased the asymmetric induction (Table 7, Entries 5 and 11). Moreover, it was established that the selectivity was highly dependent on the Pd source.[28]

An unusual effect of the temperature on the asymmetric induction was observed in these reactions. The enantioselectivity of indanone **35** from benzyl carbonate **33b** was improved from 40% to 64% *ee* by increasing the temperature from room temperature to 45 °C (Table 7, Entries 3 and 5).

Pd-Catalyzed Deprotection and EDP of Racemic Cyclic β-Oxo Esters Mediated by Chiral Amino Alcohols

Another route to prochiral enols involved the deprotection of allyl (**37a** and **38a**) and benzyl (**37b** and **38b**) β-oxo esters with $Pd(OAc)_2/PPh_3$ and Pd/C, respectively, in the presence of an amino alcohol (Figure 7). The main results are summarized in Table 8. As for the allyl enol carbonates, the deallylation required an excess of ephedrine (**C8**), and the selectivities did not exceed 50% *ee* (Table 8, Entry 1). A similar enantioselection was obtained in the debenzylation of **37b** (Table 8, Entry 2), and slight improvements were obtained with the azetidine **C18**, bearing a primary alcohol group, or cinchona alkaloids **C4** and **C6** (Table 8, Entries 3–5). The debenzylation of tetralone **38b** led to similar results (Table 8, Entries 9–12).

Table 8. Pd-catalyzed deprotection of racemic β-oxo esters and EDP.

Entry	Substrate	Base (equiv.)	Conditions[a]	Product, *ee* [%] (config.)
1[b]	**37a**	**C8** (2)	room temp., 6.5 h	**35**, 50[32]
2	**37b**	**C8** (0.3)	room temp., 4 h	**35**, 48[32]
3	**37b**	**C18** (0.3)	room temp., 7.5 h	**35**, 52 (*S*)[32]
4	**37b**	**C4** (0.3)	room temp., 2 h	**35**, 58 (S)[31]
5	**37b**	**C6** (0.3)	room temp., 2 h	**35**, 60 (*R*)[31]
6	**37b**	**C14** (0.3)	21 °C, 3.5 h	**35**, 60[27]
7	**37b**	**C14** (0.3)	52 °C, 0.58 h	**35**, >99[27]
8	**37b**	**C16b** (0.3)	55 °C, 67 min	**35**, 72[26]
9	**38b**	**C14** (0.3)	22 °C, 4 h	**36**, 45[27]
10	**38b**	**C14** (0.3)	55 °C, 0.75 h	**36**, 66[27]
11	**38b**	**C4** (0.3)	room temp., 2 h	**36**, 58 (*R*)[31]
12	**38b**	**C6** (0.3)	room temp., 2 h	**36**, 59 (*S*)[31]
13	**41**	**C14** (0.3)	22 °C, 4.5 h	**40**, 50[27]
14	**41**	**C14** (0.3)	53 °C, 0.5 h	**40**, 68[27]

[a] Reaction conditions: Pd/C (2–5 mol-%) MeCN, H_2. [b] Reaction conditions: $Pd(OAc)_2$ (5 mol-%), PPh_3 (10 mol-%), toluene.

The reaction parameters were first extensively studied by Muzart et al.[29] and more recently by Baiker et al.,[30,31] The solvent had a crucial effect on the enantioselectivity. In the debenzylation of tetralone **38b**, the highest conversions but the lowest enantioselectivities were achieved in protic polar solvents, which are less appropriate for the decarboxylation step. The selectivity was also dependent on the water content. The addition of one drop of water to the mixture of standard conditions decreased dramatically the enantioselectivity of tetralone **36**. The water content of the supported Pd could also contribute to the large differences observed among different Pd sources.[31]

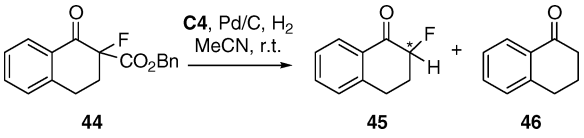
As noted before, a spectacular improvement of 40% *ee* was observed when the temperature of the debenzylation of **37b** with aminoborneol (**C14**), was raised from 21 to 52 °C (Table 8, Entries 6 and 7). This effect was also noticed in the debenzylation of oxo esters **38b** (Table 8, Entries 9 and 10) and **41** (Table 8, Entries 13 and 14). The comparison of Eyring diagram plots [ln (*R*/*S*) vs. 1/*T*] between the decarboxylation of the enol carbonate and the oxo ester showed different shapes, thus ruling out a similar mechanism of deprotection, decarboxylation and asymmetric protonation. This difference was confirmed by in situ UV monitoring of the reactions.[29]

Finally, the structure of the substrate was found to be another important parameter in the asymmetric induction. Increasing the size of the cycle of the β-oxo ester (**37b** compared to **38b**) did not modify the selectivity (Table 8, Entries 4, 5, 11 and 12). β-Oxo ester **42**, which possesses no aromatic moiety, when submitted to the standard conditions, led to ketone **43** in considerably lower enantioselectivity (Scheme 12).[31]

Scheme 12.

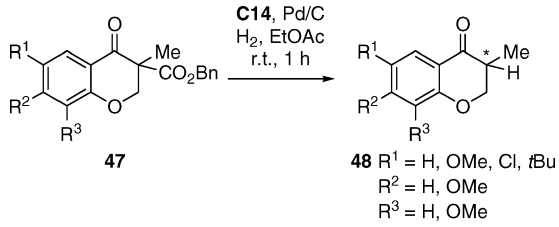
The role of Pd is limited to the deprotection of the benzyl or allyl ester (first step of the cascade reaction).[29] In order to understand the mechanism of the reaction, the β-oxo carboxylic acid intermediate **38c** was synthesized independently. Monitoring by UV spectroscopy of the Pd-catalyzed hydrogenolysis in acetonitrile of oxo esters **37b** and **38b** showed the successive formation of corresponding β-oxo acids **37c** and **38c** and the enols of ketones **35** and **36**, respectively.[29] An enantioselective enol tautomerization catalysed by the chiral amine was suggested. Recently, the kinetics of the decarboxylation of oxo acid **38c**[30] in the presence (or absence) of quinine was monitored by NMR, UV and IR spectroscopy. The studies established that Pd triggers the deprotection of **38b**, whereas the decarboxylation is catalysed by the chiral amino alcohol in the liquid phase. The kinetic resolution of the diastereomeric salts formed by racemic **38c** and the chiral amino alcohol plays a key role in the transfer of chirality. The decrease of selectivity observed when less than 2 equiv. of base was used led the authors to conclude that 1 equiv. was used for the formation of a diasteromeric complex, and the second one was responsible for the decarboxylative protonation.[33]

The catalytic EDP of 2-fluoro-β-oxo benzyl ester **44**[34] was much more sensitive to the nature of the Pd catalyst. The amino alcohols **C14**, which afforded good results with substrate **38b**, gave low enantioselectivity. Furthermore, a minor amount of the defluorinated product **46** was observed. Quinine (**C4**) was the most active base leading to **45** with up to 68% *ee* (Scheme 13).



Scheme 13.

The Pd-catalysed deprotection and EDP was applied to the synthesis of 3-substituted 4-chromanones **48** from oxo esters **47**. Among the amino alcohols tested, aminoborneol (**C14**) led to around 60–75% *ee* (Scheme 14).[35]

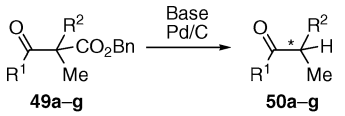


Scheme 14.

Pd-Catalyzed Deprotection and EDP of Racemic Acyclic β-Oxo Esters

The first attempts at the deprotection/EDP of acyclic β-oxo esters were disappointing.[36] The hydrogenolysis of oxo ester **49a** by Pd/C in acetonitrile with ephedrine (**C8**), aminonorborneol (**C14**) or cinchona alkaloids led to ketone **50a** in reasonable yields but with very low enantioselectivity (<17% *ee*). Furthermore, the alcohol arising from the over-reduction of **50a** was isolated. A change from **49a** to substrates **49b–f** produced improved results (Table 9).

Table 9. Pd-catalyzed deprotection and EDP of acyclic β-oxo esters.[36b]



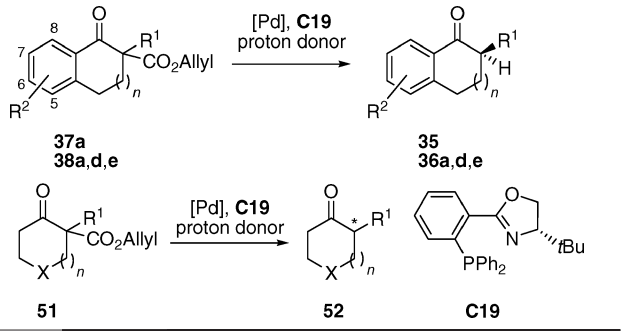
Entry		Substrate R^1	Substrate R^2	Product	*ee* [%] (config.)
1	**49a**	Ph	Bn	**50a**[a]	10 (*S*)
2	**49b**	Ph	Ph	**50b**[b]	71 (*S*)
3	**49c**	Ph	4-$MeOC_6H_4$	**50c**[b]	75 (*S*)
4	**49d**	Ph	4-MeC_6H_4	**50d**[b]	71 (*S*)
5	**49e**	Ph	4-PhC_6H_4	**50e**[b]	72 (*S*)
6	**49f**	Ph	4-FC_6H_4	**50f**[b]	66 (*S*)
7	**49g**	Me	Ph	**50g**[a]	67 (*R*)

[a] **C3** (30 mol-%) was used in MeCN. [b] Reaction conditions: **C5** (30 mol-%), Pd/C (2.5 mol-%), H_2, EtOAc, room temp., 1–2 h.

Pd-Catalyzed Deprotection and EDP of Racemic Cyclic β-Oxo Esters Mediated by a Chiral Phosphane

The EDP of allyl β-oxo esters described previously were limited in substrate scope, and few were catalytic in chiral sources. With the chiral phosphanyloxazoline **C19** (Table 10) as a Pd ligand, Stoltz et al.,[37,38] succeeded in obtaining indanone **35** and tetralone **36** in the decarboxylation of allyl esters **37a** and **38a**, respectively (Table 10, Entries 1 and 4), with high enantioselectivity.

Table 10. Pd-catalyzed EDP with formic acid.[a]



Entry	Substrate	*n*	R^1	R^2 or X	Product, *ee* [%] (config.)
1	**38a**	1	Me	H	**36a**, 94 (*S*)
2	**38d**	1	allyl	H	**36d**, 85 (*R*)
3	**38e**	1	F	H	**36e**, 88 (*S*)
4	**37a**	0	Me	H	**35**, 81 (*S*)[b]
5	**51a**	0	Bn	CH_2	**52a**, 60
6	**51b**	1	Me	CH_2	**52b**, 85 (*R*)
7	**51c**	1	Bn	CH_2	**52c**, 92 (*S*)[c]
8	**51d**	2	Bn	CH_2	**52d**, 74
9	**51e**	1	Et	NHBn	**52e**, 84

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol-%), **C19** (12.5 mol-%), HCO_2H (5–8 equiv.), MS (4 Å), dioxane, 40 °C, 0.3 mmol scale. [b] $Pd(OAc)_2$ (5 mol-%), **C19** (6.25 mol-%). [c] Performed at 35 °C.

Careful optimization of the amounts of molecular sieves (4 Å) and formic acid was necessary to suppress the competitive allylation and to maximize the enantioselectivity. The scope of the reaction is large. A few examples are given for comparison of the efficiency of the asymmetric induction (Table 10, Entries 2, 3, 5 and 9). The mechanism of the proton incorporation remained unclear in spite of deuteration experiments.

In a subsequent report, various achiral organic proton donors were tested. It was found that their acidic property has an important impact on the selectivity.[38] The more acidic compounds increased the rate of the reaction dramatically, and Meldrum's acid was the most efficient in terms of enantioselectivity. Table 11 shows some results that can be compared with those obtained previously (Table 10). A slight erosion of the enantioselectivity was noticed upon scaling up the reaction (Table 11, Entry 5).

Kinetic studies suggested that the β-oxo ester reacts very fast and generates an intermediate (Pd carboxylate or Pd enolate) that undergoes further reaction in a slower step.[38]

Table 11. Pd-catalyzed EDP with Meldrum's acid.[a]

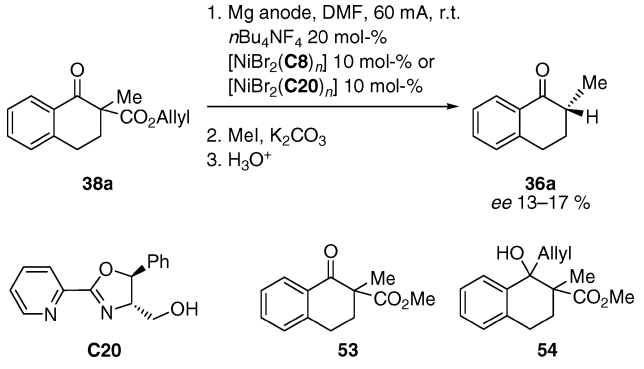
Entry	Substrate	*n*	R^1	R^2 or X	Product, *ee* [%] (config.)
1	**51b**	1	Me	CH_2	**52b**, 88 (*R*)
2	**51c**	1	Bn	CH_2	**52c**, 83 (*S*)
3	**38a**	1	Me	H	**36a**, 90 (*S*)
4	**38d**	1	allyl	H	**36d**, 82 (*R*)
5	**37a**	0	Me	H	**35**, 61 (*S*)[b]

[a] Reaction conditions: $Pd_2(dba)_3$ (5 mol-%), **C19** (12.5 mol-%), Meldrum's acid (2.5 equiv.), dioxane, 22 °C, 0.1 mmol scale. [b] 0.3 mmol scale.

With this methodology, the synthesis of a variety of α-tertiary cycloalkanones **35**, **36** and **52** were prepared with high enantioselectivity.

Electrochemical Deprotection and EDP of a Racemic β-Oxo Allyl Ester Mediated by Nickel Complexes

A single article reports an attempted nickel-mediated EDP. The electroreduction of oxo ester **38a** was carried out under mild conditions with an Mg anode and catalytic quantities of chiral nickel(II) complexes. However, modest selectivities of decarboxylated **36** were obtained with complexes of ephedrine (**C8**) and oxazoline **C20** (Scheme 15). Moreover, substantial amounts of side-products **53** and **54** were also formed.[39]



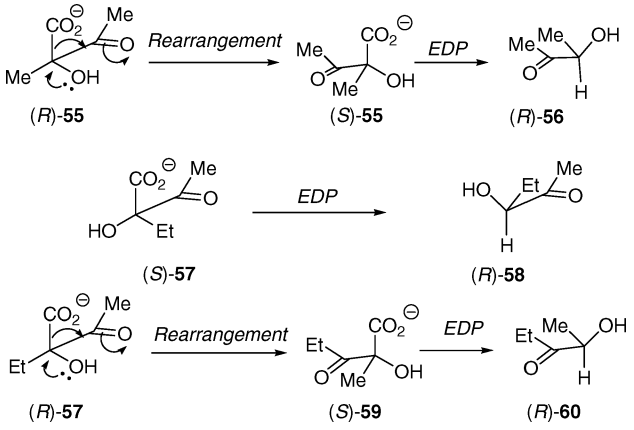
Scheme 15.

EDP Catalysed by Enzymes

Biocatalysed reactions have been used for the synthesis of enantiomerically pure compounds.[40] A few enzymes or microorganisms are known to catalyse the EDP of specific substrates. Under those conditions, EDP reactions can be considered as asymmetric protonations of a "carbanion equivalent" in aqueous medium. The hydrophobicity of the active site prevents the bulk water molecules from participating in the reaction inside the enzyme.[41] Among the variety of known decarboxylases, arylmalonate decarboxylase and serine hydroxymethyltransferase are specific to EDP.

EDP Mediated by Acetolactate Decarboxylase (ALD)

Acetolactate decarboxylase [EC 4.1.1.5] (ALD), isolated from *Aerobacter aerogenes*, catalyses the decarboxylation of racemic 2-hydroxy-2-methyl-3-oxobutanoate (**55**, α-acetolactate) to (3*R*)-hydroxybutanone **56**. The (*S*) isomer is the preferred substrate of the enzyme, and the decarboxylation of this enantiomer proceeds with overall inversion of configuration. The (*R*) isomer is also decarboxylated but at a lower rate and affords the same enantiomer, (*R*)-**56**. This was attributed to the isomerisation of (*R*)-**56** to its enantiomer (*S*)-**56** by a benzoin-type rearrangement (migration of the carboxylate group) prior to the decarboxylation. Under the same conditions, racemic 2-ethyl-2-hydroxy-3-oxobutanoate (**57**) yielded a mixture of (*R*)-ketols **58** and **60** (93 and 95% *ee*, respectively, Scheme 16).[42]

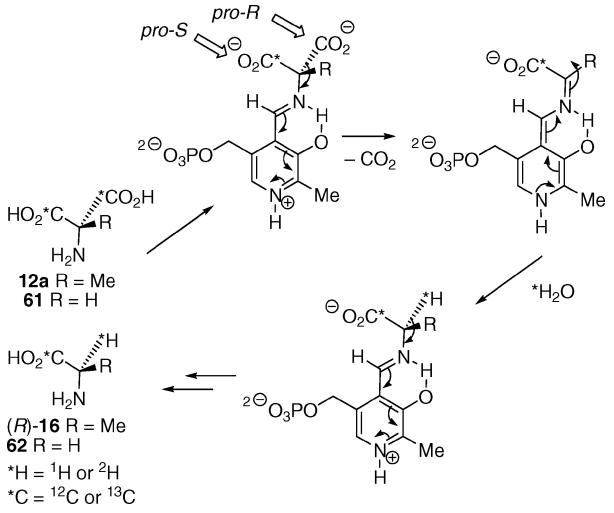


Scheme 16.

EDP Mediated by Serine Hydroxymethyltransferase (SHMT)

Serine hydroxymethyltransferase (SHMT) is a ubiquitous pyridoxal 5′-phosphate dependent enzyme, which is able to catalyse a variety of reactions including the decarboxylations of appropriate substrates.[43] 2-Amino-2-methylmalonic acid (**12a**) and both of its [1-^{13}C] enantiomers were used to probe the stereochemical course and mechanism of SHMT-catalysed reactions. The EDP reaction was stereospecific; the [^{13}C]-carboxyl group of labelled acid (*R*)-[1-^{13}C]-**12a** was replaced by a proton with retention of configuration at C-2 to give unlabelled (2*R*)-alanine (**16**), whereas (*S*)-[1-^{13}C]-**12a** led to (2*R*)-[1-^{13}C]-**16**.

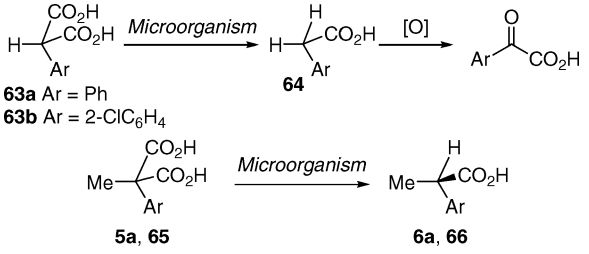
The decarboxylation of aminomalonic acid (**61**) was also extensively studied.[44] The stereoselectivity of the reaction was unambiguously proven by incubating acid **61** with rabbit liver cytosolic SHMT in deuterated buffer. The ratio of the enantiomers of [2-^{2}H]-glycine (**62**) was determined from the ^{1}H NMR spectra of their (1*S*,4*R*)-camphanamides. Under conditions avoiding H exchange and racemisation, (*S*)-[2-^{2}H]-glycine (**62**) was the only stereoisomer formed. When the same experiment was performed with H_2O, only (*R*)-[2-^{2}H]-glycine (**62**) was formed. These experiments suggested that the decarboxylative protonation of **61** occurred with retention of configuration (Scheme 17).



Scheme 17.

EDP Mediated by Arylmalonate Decarboxylase (AMDase)

Ohta et al. developed the synthesis of chiral acids from malonic acids with arylmalonate decarboxylase (AMDase),[41,45,46] which was recently crystallised and characterized by X-ray diffraction.[47,48] The concept was based on the initial observation that some microorganisms are able to grow with phenylmalonic acid as the sole source of carbon. The first step of metabolism is a decarboxylation, affording phenylacetic acid, which is then oxidized. If disubstituted malonic acids were treated with the same microorganisms (the oxidation step being not possible), the chiral acid should accumulate in the medium (Scheme 18).

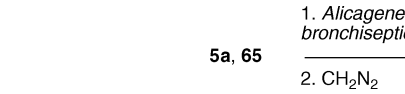


Scheme 18.

Among the variety of microorganisms tested, *Alicagenes bronchisepticus* was found to transform methyl(phenyl)malonic acid (**5a**) into phenylpropionic acid (**6a**), isolated in high yield and enantioselectivity as its methyl ester after diazomethane esterification (Table 12).

The scope of the reaction was studied (Table 12 and Figure 8).[49,50] Generally, the yields were higher when the substituents on the aromatic ring were strongly electron-withdrawing (Table 12, Entries 5, 8 and 10–12 compared to Entries 2 and 3). We note that the *ortho*-substituted aryl derivatives gave no reaction (Table 12, Entries 4 and 6) or poor yield and enantioselectivity (Table 12, Entry 9). These results suggested that *ortho* substituents inhibit the reaction. 3-Fluoro (**65f**), 4-fluoro (**65g**) and 4-chloro (**65d**) derivatives afforded the expected propionic esters in high enantioselectivity and in moderate to high yields (Table 12, Entries 7, 8 and 5). When the first substituent of the malonic acid was an aryl group, only a methyl group (**5a**, **65**), a fluorine atom (**67**) or an ethylidene chain (**68**) were tolerated as second substituents. 2-Methyl-2-benzylmalonic acid (**71**) or its heteroatom derivatives gave no reaction on incubation with the isolated enzyme. Finally, the enzyme was specific for the prochiral malonic acid. Indeed, no reaction was observed with the racemic monoethyl ester of **17a**.[45]

Table 12. Scope of the EDP of aryl(methyl)malonic acids mediated by AMDase.



Entry	Product	Ar	Yield [%]	*ee* [%]
1	**6a**	Ph	80	98
2	**66a**	4-$MeOC_6H_4$	48	99
3	**66b**	4-MeC_6H_4	44	>95
4	**66c**	2-MeC_6H_4	0	
5	**66d**	4-ClC_6H_4	95	>95
6	**66e**	2-ClC_6H_4	0	
7	**66f**	3-FC_6H_4	75	97
8	**66g**	4-FC_6H_4	54	97
9	**66h**	2-FC_6H_4	12	54
10	**66i**	3-$F_3CC_6H_4$	99	>95
11	**66j**	2-thienyl	98	95
12	**66k**	6-MeO-2-naphthyl	96	>95

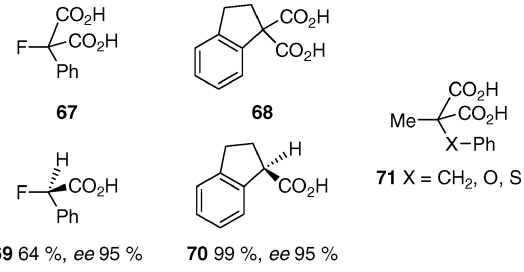


Figure 8. Other substrates incubated with AMDase and their products.

The effect of conformation of substrate on the enzymatic decarboxylation of malonic acids **65e** and **63b** was studied.[50,51] From the experimental results showing that the *ortho*-substituted derivatives **65c** and **65e** were not decarboxylated by the enzyme, it was suggested that a *syn*-periplanar conformation (**A** in Figure 9) was required for substrate binding to the enzyme active site. This conclusion was supported by theoretical calculations and kinetic studies. In the indane derivative **68**, the conformation is fixed as *syn*-periplanar, and thus, decarboxylation occurred in high yield and enantioselectivity (Figures 8 and 9).

The stereochemical course of the enzymatic decarboxylation was studied. By labelling either the *pro*-(*R*)- or the *pro*-(S)-carboxyl group with ^{13}C, Ohta et al.[51] showed that the *pro*-(*R*)-carboxyl group of methyl(phenyl)malonic acid was eliminated to form (*R*)-phenylpropionic acid with inversion of configuration (Scheme 19).

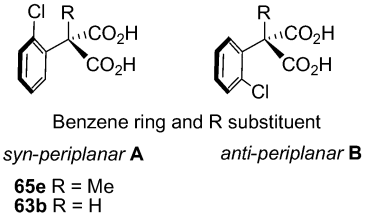
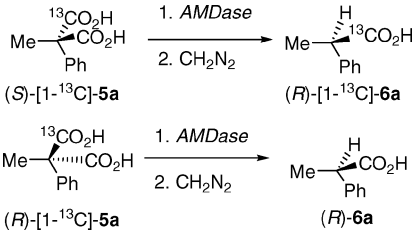
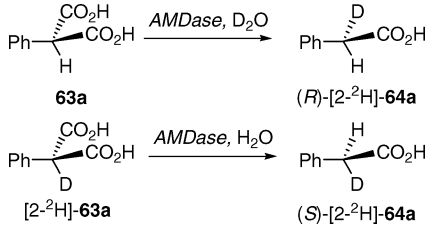


Figure 9. Possible planar conformations of aryl-substituted malonic acids.



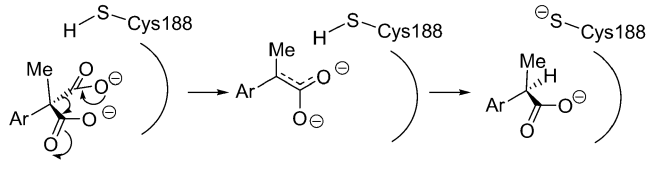
Scheme 19.

The high stereoselectivity observed was used to synthesize both enantiomers of [2-^{2}H]-phenylacetic acid by treating either [2-^{2}H]-phenylmalonic acid with the aqueous purified enzyme (AMDase) or phenylmalonic acid with the enzyme in D_2O (Scheme 20).[52]



Scheme 20.

Deep insight into the reaction mechanism of the asymmetric decarboxylation of a 2-aryl-2-methylmalonic acid into an (*R*)-2-arylpropionic acid catalyzed by AMDase, was provided by directed mutagenesis studies.[53] Based on the comparison of the pH-rate profiles of the native enzyme with the C188Ser mutant and on the homology of ADMase with racemases, it was suggested that Cys188 delivers a proton to the *si* face of the enolate intermediate, resulting in the formation of a single enantiomer (Scheme 21).



Scheme 21.

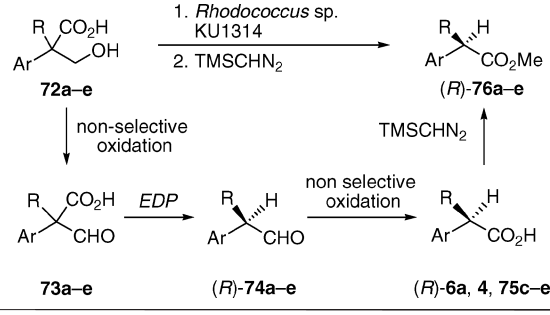
If this role for Cys188 is true, the introduction of a cysteine residue around the region supposedly located on the opposite side of the substrate from Cys188 might result in the lowering or inversion of the enantioselectivity. This hypothesis was tested with the Gly74Cys/Cys188Ser mutant. With this enzyme, an inversion of the enantioselectivity was observed, but the activity was much lower than that of the native enzyme.[54] The introduction of a single mutation was also able to change the arylmalonate decarboxylase activity to that of a racemase.[55] With the aim of increasing both the enantioselectivity and the activity, each amino acid between residues 68 and 77 was replaced with cysteine. Among the ten mutants prepared, two (S71C/C188S and G74C/C188S) exhibited a decarboxylation activity with an opposite enantioselectivity compared to that of the wild-type enzyme.[56] Recently, a dioxy anion hole was postulated as a key element in the stabilisation of the enediolate intermediate.[57] The AMDase would orient the malonate substrate in such a way that one carboxyl group would be strongly stabilised by an H-bonding network, whereas the other carboxylate group would be tightly bound in a small hydrophobic pocket without any stabilizing electrostatic interactions. Moreover, the cavity is shaped for binding aromatic groups with van der Waals interactions. The aryl chain would remain co-planar with the enediolate, ensuring a stabilizing effect by delocalising the negative charge.

EDP of Malonic Semialdehyde Mediated by *Rhodococcus* sp. KU1314

Based on the transformation of 2-(hydroxymethyl)-2-phenylpropionic acid to phenylacetic acid through phenylacetaldehyde by microorganisms, Ohta et al.[58] studied the conversion of 2-substituted 2-aryl-3-hydroxypropionic acids into 2-substituted 2-arylacetic acids mediated by *Rhodococcus* sp KU1314.

Under optimal experimental conditions, hydroxy acids **72a**–**e** were submitted to the enzymatic reaction (Table 13). Replacement of a methyl group by an ethyl group induced a dramatic decrease in the yield, but with the highest enantioselectivity (85% *ee*) obtained in the series (Table 13,

Table 13. EDP of malonic semialdehydes mediated by a microorganism.



Entry	Product	Ar	R	Yield [%]	*ee* [%]
1	**76a**	Ph	Me	61	68
2	**76b**	Ph	Et	25	85
3	**76c**	4-$MeOC_6H_4$	Me	61	74
4	**76d**	4-ClC_6H_4	Me	75	0
5	**76e**	2-naphthyl	Me	60	48

compare Entries 1 and 2). With the other substrates (**72c**–**e**) the yields were good, but the enantioselectivity was moderate. In the case of the 4-chlorophenyl derivative, the product **76d** was racemic. The authors supposed that the intermediate aldehyde **74d** racemised quickly due to the higher acidity of the proton α to the aldehyde group. The enzymatic reaction performed with each enantiomer of hydroxy acid **72a** demonstrated unambiguously that the asymmetric step is the decarboxylative protonation, and the oxidation was non-selective.

Conclusions

We have presented the first review of EDP as an efficient route to enantioenriched α-amino acids and ketones from malonic acids or esters, enol carbonates or β-oxo esters. To summarize the main advances in the field, an organocatalytic approach to the decarboxylative protonations (base-mediated reaction) was successfully used for the synthesis of amino acids or related compounds. The highest yields and enantioselectivities (93% *ee*) reported for any organic base used a chiral thiourea derived from quinine. However, under the conditions used (0 °C, polar aprotic solvent), the catalytic activity needs to be improved in order to decrease the reaction time. Recently, ketones with a high enantioselectivity (up to 94% *ee*) were obtained in the Pd-catalyzed deprotection and EDP of β-oxo esters with a chiral ligand. Elegant studies on the decarboxylation of malonic acids with decarboxylases were reported. The highest enantioselectivities (>95% *ee*) were obtained with *Alicagenes brochisepticus*, and the reaction was very sensitive to steric and electronic effects. Very recently, some mechanistic studies on Pd- and enzyme-mediated reactions were reported. A greater understanding of the in-depth mechanism associated with each chemical approach would likely allow the rational design of more efficient catalysts.

The use of this reaction for the synthesis of compounds of biological significance is already emerging. This highlights the synthetic potential of this old, simple and low-cost reaction, notably in the context of sustainable chemistry. However, the enantioselective version of the malonic (or acetoacetic acid) synthesis is not yet mature, and many studies need to be performed to make this reaction general, practical and useful for the synthesis of complex structures. The goal of this comprehensive review was to trigger interest not only in the reader but mainly the experimentalist for this little developed reaction in order to expand its scope, which remains a challenging area.

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