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Tetrahedron
Tetrahedron 62 (2006) 6155–6165

Organocatalyzed route to enantioenriched pipecolic esters: decarboxylation of an aminomalonate hemiester

Thomas Seitz,[a] Jérôme Baudoux,[b] Henri Bekolo,[a] Dominique Cahard,[b] Jean-Christophe Plaquevent,[b] Marie-Claire Lasne[a] and Jacques Rouden[a,*]

[a]*Laboratoire de Chimie Moléculaire et Thio-organique, UMR CNRS 6507—ENSICAEN, Université de Caen-Basse Normandie, 6 Boulevard du Maréchal Juin, 14050 Caen Cedex, France*
[b]*IRCOF, UMR CNRS 6014—Université de Rouen, Faculté des Sciences, Rue Tesnière, 76821 Mont Saint Aignan Cedex, France*

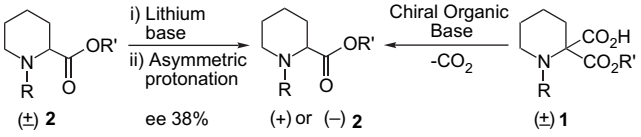
Received 3 April 2006; revised 14 April 2006; accepted 20 April 2006
Available online 8 May 2006

Abstract—Enantioenriched pipecolic esters were prepared in good yields in the decarboxylation, at room temperature, of *N*-protected piperidinohemimalonates catalyzed by cinchona alkaloids. Enantiomeric excesses as high as 72% were obtained when using 9-*epi*-cinchonine and the *N*-benzoyl substituted piperidinohemimalonate. A detailed study of the different reaction parameters revealed that the selectivity of this noncovalent organocatalyzed reaction is strongly dependent on the solvent, toluene or carbon tetrachloride being the best ones. The whole process based on the malonic acid synthesis was successfully tested on a 10 mmolar scale and established a practical alternative to the asymmetric protonation of lithium enolates.

1. Introduction

Organocatalysis,[1] which is the acceleration of chemical reactions with a substoichiometric amount of an organic compound is a well-known concept in living systems since many organic reactions are catalyzed by metal-free enzymes, eventually inducing a high level of asymmetry. In recent years it has been established that much smaller chiral organic molecules are able to achieve comparable performances.[2] Although remarkable results in asymmetric organocatalytic reactions were reported in the sixties and seventies,[3] these works were overlooked until recently, by the prominence of transition-metal-catalyzed asymmetric transformations. Today, due to environmental concerns, there is a need for metal-free chemistry. As a consequence, organocatalysis has emerged as a new tool to efficiently perform organic reactions with high enantioselectivity under very mild and simple conditions.

As part of a program on the synthesis of a selective M_2 muscarinic receptor antagonist,[4] we developed an efficient enantioselective route to pipecolamides (ee's: 95–99%) in order to have access to both enantiomers.[5] It was based on the asymmetric protonation of a lithium enolate. However, attempts to use this methodology to prepare the corresponding esters afforded ee's lower than 40%.[6] Moreover, the deracemization used capricious *sec*-butyl lithium, required low and difficult-to-adjust temperatures, and stoichiometric amounts of the chiral reagent. Therefore, we considered the asymmetric decarboxylation of a malonyl analogue of pipecolate as an organocatalyzed alternative to the chiral protonation of pipecolyl enolates (Scheme 1).



Scheme 1. Asymmetric protonation versus asymmetric decarboxylation.

The first example of an enantioselective decarboxylation was reported by Marckwald in 1904.[7] For more than 70 years this reaction received little attention.[8] In the seventies and eighties, metal-mediated asymmetric decarboxylations were developed. First, stoichiometric amounts of chiral cobalt–amine complexes were shown to induce high level of enantioselectivity in the decarboxylation of α-alkyl-α-aminomalonic acids.[9] In 1987, Maumy used a catalytic combination of copper(I) and cinchonidine to promote the asymmetric decarboxylation of a monoalkyl phenylmalonate hemiester with an ee of 31%.[10] Later, based on Darensbourg's work,[11] Brunner's group[12] and then Hénin–Muzart[13] proved that copper was not necessary, thus developing the first organocatalytic asymmetric decarboxylations.

Keywords: Organocatalysis; Enantioselective decarboxylation; Pipecolate; Cinchona alkaloids.
* Corresponding author. Tel.: +33 131452893; fax: +33 131452877; e-mail: jacques.rouden@ensicaen.fr

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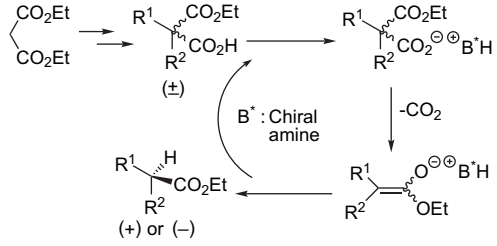
doi:10.1016/j.tet.2006.04.062

Then, Brunner studied the decarboxylation of an α-cyanocarboxylic acid and of 2-aminomalonic acid derivatives with chiral bases. Enantiomeric excesses (ee's) up to 72% were reached.[14] More than 25–30 chiral bases derived mainly from the 9-*epi* configuration of the parent alkaloid were tested. The role of the C9 configuration of the alkaloid was not investigated. Related to this organocatalyzed reaction are the palladium-induced enantioselective debenzylation–decarboxylation.[15] Finally, a decarboxylase, isolated from a bacterium strain, was shown to catalyze the enantioselective decarboxylation of arylalkylmalonic acids with ee's up to 97%.[16] The main drawback of these reagents remains their high degree of specificity for the substrate.[17]

In this paper we described our extensive work on the asymmetric decarboxylation of malonyl pipecolates **1** catalyzed by cinchona alkaloids to synthesize enantiomerically enriched pipecolate ester **2** (Scheme 1). The selectivity of the reaction was studied as a function of different reaction parameters (solvent, concentration, temperature), of the substrate (nitrogen substituent) and of the organic base. We examined also the effect of inversion of configuration at C9 of cinchona derivatives on the catalyst performance.

2. Results and discussion

The malonic acid synthesis is a classical but yet a useful method for the synthesis of α,α′-disubstituted carboxylic acids. The principle of the organocatalyzed asymmetric malonic acid synthesis is depicted in Scheme 2. Sequential alkylations followed by monosaponification of a malonate ester generate a racemic acid–ester, which is subjected to the decarboxylation in the presence of a chiral base.



Scheme 2. Organocatalyzed asymmetric decarboxylation.

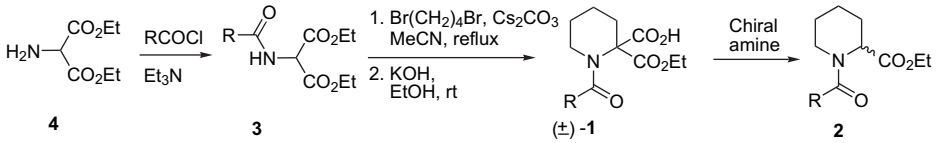
When using an optically pure amine, we expect a rapid deprotonation of the carboxylic acid by the amine resulting in the formation of a diastereoisomeric mixture of salts. Then, in appropriate conditions (solvent, temperature) the unstable carboxylate looses carbon dioxide affording an intermediate enolate, which should be rapidly protonated to generate an enantiomerically enriched α-substituted ester. On the asymmetric point of view, the chirality of the product is introduced at the final step and the whole process resembles the enantioselective protonation of enolates.[18] According to the pK_a of the species involved in this route, a catalytic amount of an enantiomerically pure amine as chiral organic catalyst can be used.[14] Moreover, the protonation step should be an irreversible process under the reaction conditions and the optical activity of the product should not be altered by any of the other species.

2.1. Evaluation of the reaction parameters

Compound **1a** was easily synthesized from commercially available acetamido malonate **3a**. Preliminary investigations showed that triethylamine was able to promote the decarboxylation under simple and mild conditions to generate **2a**. Several chiral amines were screened and cinchona alkaloids were the most efficient bases to induce asymmetry.[19] The study of the different reaction parameters on the enantioselectivity was undertaken with **1b**, easily detected by HPLC, and prepared in a three-step sequence starting from aminomalonate **4** (Scheme 3).

The optically pure pipecolates **2** were prepared independently and fully characterized in order to determine the enantiomeric excess and absolute configuration of the enantiomers formed in asymmetric decarboxylations. In our first experiments, the reactions were conducted in THF, the solvent of choice for the decarboxylations.[14] A quick survey of the four commercially available cinchona alkaloids revealed that cinchonine (**CN**), used in a 1/1 ratio with **1b**, induced the best ee of 33%. Therefore, **CN** was selected as the base for the study of the different reaction parameters on the efficiency and enantioselectivity of the reaction (Table 1).

This first set of data showed that the temperature, the concentration and the amount of base used have no significant influence on the enantioselectivity of the decarboxylation, at least in the ranges studied. The conversion of the reaction was decreased at 0 °C or when a substoichiometric amount of **CN** was used (entries 4 and 7). The effect of the temperature deserves some comments: on one hand, there was no gain of selectivity while cooling down the reaction to 0 °C. Below this temperature, one would expect such a slow rate for the decarboxylation that the reaction would loose its original benefit. On the other hand, heating the mixture to 60 °C did not affect the selectivity while increasing the



4

3

R	Yield (%)
a Me-	-
b Ph-	88
c *p*-MeOC$_6$H$_4$-	81
d *p*-NO$_2$C$_6$H$_4$-	62
e α-Naphyl	91

(±) **-1**

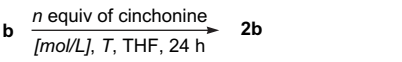
R	Yield (%)
a Me-	65
b Ph-	38
c *p*-MeOC$_6$H$_4$-	45
d *p*-NO$_2$C$_6$H$_4$-	39
e α-Naphyl	23

2

R
a Me-
b Ph-
c *p*-MeOC$_6$H$_4$-
d *p*-NO$_2$C$_6$H$_4$-
e α-Naphyl

Scheme 3. Synthesis of substrates.

Table 1. Decarboxylation of **1b**: ee's as a function of concentration, temperature and the amount of base



Entry	[**1b**] (mol/L)	T (°C)	n	Yield (%)[a]	ee (%)[b]
1	0.01	20	1	88	34
2	0.025	20	1	91	33
3	0.05	20	1	96	34
4	0.05	0	1	70	34
5	0.05	60[c]	1	89	37
6	0.05	20	2	83	36
7	0.05	20	0.5	65	36

[a] Isolated yields.
[b] Determined by chiral HPLC. The (*R*) product was obtained as the major enantiomer.
[c] Complete conversion after 12 h.

reaction rate as already observed by Brunner (entry 5).[14] Therefore the effect of a substoichiometric amount of the alkaloid (entry 7) could be compensated by a slight increase of the temperature to keep the reaction time in a reasonable scale.

The choice of the solvent is an important issue in organocatalysis. Acetonitrile was the solvent used for metal-mediated asymmetric decarboxylations[10,12] and THF was preferred in the few examples of organocatalytic decarboxylations.[14] From Table 1, we selected our conditions for studying the effect of the solvent on the enantioselectivity of the reaction. In order to have a complete reaction in 24 h at room temperature, we chose to use **1b** and **CN** (1 equiv) at a concentration of 0.05 mol/L (Table 2).

A strong influence of the solvent on the enantioselectivity of the decarboxylation was observed. The ee's were moderate in THF, poor in the more polar CH_3CN and very low in ionic liquid ([bmim]PF_6), whereas they reached 61–63% in nonpolar solvents like toluene or CCl_4.[20] Unlike in Brunner's work,[14] even though the reaction partners were only slightly soluble in those solvents, a very good conversion and a good level of selectivity were observed. In the nonpolar solvents cyclohexane and perfluorocyclohexane, both the enantioselectivity and the conversion decreased dramatically (entries 10 and 11). This could be due to the insolubility of the reaction components in the used solvents. However, to confirm the tendency observed in Table 2 for other substrates and amines we decided to pursue the study by carrying out each decarboxylation separately in two different solvents. CCl_4 was the solvent giving here the best selectivity and THF was the solvent, which gave the best results in Brunner's work. At this point, we checked for the possibility of having a deracemization[21] of the *N*-benzoylpipecolate **2b**, after decarboxylation–protonation of compound **1b**. Therefore we mixed racemic product **2b** with a stoichiometric amount of **CN** in CCl_4 and heated the solution at 70 °C for three days. We applied the same conditions to enantiopure product **2b** synthesized independently. In both the cases no change of the ee's occurred.

Table 2. Decarboxylation of **1b**: solvent effect on the ee of **2b**

Entry	Solvent	υ[a]	ε[b]	Yield (%)[c]	ee (%)[d]
1	[bmim]PF_6	>5	30–40	88	17
2	CH_3CN	3.9	37.5	91	21
3	THF	1.7	7.5	96	33
4	CH_2Cl_2	1.6	9.0	70	46
5	$CHCl_3$	1.2	4.8	89	45
6	Et_2O	1.1	4.3	85	52
7	*Toluene*	*0.4*	*2.4*	*91*	*61*
8	1,4-Dioxane	0	2.2	87	43
9	*CCl_4*	*0*	*2.2*	*92*	*63*
10	Cyclohexane	0	2.0	62	45
11	C_6F_{12}	0	—	61	19

[a] υ: Dipolar moment.
[b] ε: Dielectric constant.
[c] Isolated yield.
[d] Determined by chiral HPLC. The (*R*) product was obtained as the major enantiomer.

2.2. Screening cinchona alkaloid analogues on the decarboxylation of malonate hemiesters 1

In a first step towards the optimization of the selectivity, we synthesized various substrates and bases. Concerning the starting hemiesters **1**, we focused on the piperidine protected by an aroyl group starting from the initial observation that a benzoyl group clearly improved the selectivity compared to an acetyl group.[22] Precursors **1c–e** (Scheme 3) bearing *para*-methoxy, *para*-nitrobenzoyl or α-naphtoyl substituent on the piperidine nitrogen atom were thus prepared. The cinchona alkaloid structure was kept as a common scaffold for the bases, changing only the nature and the configuration of the functional group at C9. All used chiral bases are presented in Figure 1 and were either synthesized according to literature procedures[14,23] or by using classical reactions. All compounds derived from quinidine (**QD**) and cinchonine (**CN**), which have the same configurations at C8 and C9 (8*R*, 9*S*) and for some of these, we also prepared the C9 epimer [along this article '*epi*' refers to the configuration C9 (*R*)]. These bases bear at C9 different functional groups (alcohol: '**QD**' and '**CN**', ether: '**OMe**', benzamide: '**Amide**', phenylcarbamate: '**PhCarb**' or *tert*-butylcarbamate: '***t*-BuCarb**'). We also tested bis-alkaloids **(DHQD)$_2$PYR**, **(DHQD)$_2$AQN**, **(CN)$_2$PYR** and cyclic ethers ('**Cyclic**').

Because of the crucial role of the solvent, the decarboxylation of the *N*-acetyl derivative **1a** with the whole set of bases was reinvestigated in several solvents. The two most significant results were obtained in Et_2O by using bases **QD** and **QD–Amide** with ee's, respectively, of 36% and 33%. With the other bases or solvents, the enantioselectivity of the reaction was consistently lower than 30%, not sufficient to draw any conclusions regarding the relation structure–enantioselectivity of the base.[24]

The main results of the decarboxylation, in carbon tetrachloride or in THF, of *N*-benzoylated substrate **1b** in the presence of some of the bases shown in Figure 1, are summarized in Table 3. They show the dramatic influence of the methoxy group on the quinoline ring (i.e. quinidine or cinchonine as the parent alkaloids). The ee's in Table 3, which were obtained with six different bases derived from quinidine **QD** (entries 1–3, 5 and 6), are low with the exception of the one obtained with the bis-alkaloid **(DHQD)$_2$PYR** (entry 4). The decrease of the selectivity is intriguing considering the remote distance on the base of the methoxy group from the nitrogen of the quinuclidine ring. The ee's obtained with bases derived from cinchonine are much higher, reaching 72%

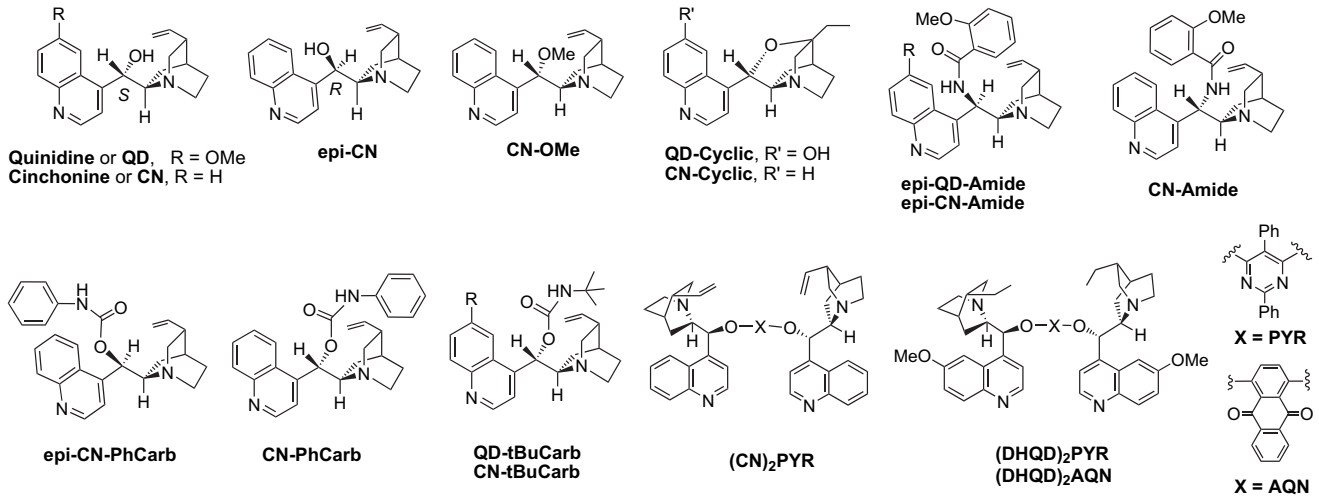


Figure 1. Cinchona derivatives used as bases.

Table 3. Decarboxylation of **1b** with cinchonine and quinidine type alkaloids[a]

Entry	Base	C_9	ee % (configuration)[c]	
			CCl_4	THF
1	**QD**	*S*	18 (*S*)	18 (*R*)
2	*epi*-**QD–Amide**[b]	*R*	9 (*S*)	0
3	**QD**–*t*-**BuCarb**	*S*	7 (*S*)	—
4	**(DHQD)$_2$PYR**	*S*	*64* (*S*)	50 (*S*)
5	**(DHQD)$_2$AQN**	*S*	9 (*S*)	—
6	**QD–Cyclic**	*S*	—	2 (*R*)
7	**CN**	*S*	*64* (*R*)	33 (*R*)
8	*epi*-**CN**	*R*	*72* (*R*)	*66* (*R*)
9	**CN**–*t*-**BuCarb**	*S*	50 (*S*)	39 (*S*)
10	**CN–PhCarb**	*S*	17 (*R*)	6 (*R*)
11	*epi*-**CN–Amide**[b]	*R*	42 (*S*)	42 (*S*)
12	**CN–Amide**[b]	*S*	9 (*S*)	—
13	**(CN)$_2$PYR**	*S*	*63* (*S*)	—
14	**CN–OMe**	*S*	10 (*R*)	—
15	**CN–Cyclic**	*S*	11 (*S*)	19 (*S*)

[a] Reaction conditions: 0.1 mmol of **1b** and 0.1 mmol of the base were left at room temperature for 24 h.
[b] Reactions were carried out for three days.
[c] Absolute configuration of the major enantiomer. ee's were measured by chiral HPLC.

with *epi*-**CN** in CCl_4 (entry 8). However, the correlation between the selectivity, the absolute configuration of the major enantiomer and the configuration of the base at C9 deserves some preliminary comments.

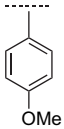
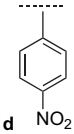
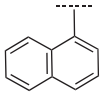
For example, **CN** and *epi*-**CN** induced in CCl_4 similar ee's (entries 7 and 8) and the same enantioselectivity, in favour of the *R* product. However, *epi*-**CN–Amide** gave a reasonable enantioselectivity in favour of the *S* product but opposite to that of *epi*-**CN** (entries 7 and 11). Another surprising result was the comparison between **CN**–*t*-**BuCarb** favouring the *S* product whereas **CN**, having the same absolute configuration, generated mainly the *R* product (entries 9 and 7). More generally, a simple relation between the absolute configuration of the base at C9 and the major enantiomer obtained cannot be established, even when considering only significant results (above 40–50% ee).

Noteworthy is the comparison between the base developed by Brunner, namely (9*R*)-*epi*-**CN–Amide**, and its epimeric analogue (9*S*)-**CN–Amide**: when having an amide group on the C9 of the base, only the 9*R* configuration (*epi*-**CN–Amide**) is able to induce a good level of selectivity, a point not previously addressed. Interestingly, bis-alkaloids derived from **QD** or **CN** (same configuration at C9) with a diphenylpyrimidine linker, **(DHQD)$_2$PYR** or **(CN)$_2$PYR**, were able to induce the same and good enantioselectivity but opposite to that of **CN** (entries 4 and 13). We did not observe the same deleterious effect on the selectivity from the methoxy group on the quinoline moiety as mentioned previously with monoalkaloids since the value of the ee obtained for pipecolate **2b** with **(DHQD)$_2$PYR** or **(CN)$_2$PYR** is identical to the one obtained with **CN** in CCl_4. Finally, the decarboxylations catalyzed by ether derivatives of **CN**, **CN–Cyclic** or **CN–OMe**, gave nearly racemic mixtures of **2b**. These results point out the role of the hydroxyl group of **CN** in the overall chiral induction process. From all the data presented in Table 3, one can conclude that the highest enantioselectivity can be reached when the piperidine was protected with a benzoyl group (compared to an acetyl) and when there is no methoxy group on the quinoline ring of the base.

We pursued the study by varying the electronic nature and the size of the aromatic ring on the piperidine substituent to strengthen the π-stacking interactions. Compounds **1c**–**1e** were tested with the **CN** derivatives (Table 4).

The ee's obtained with the *N*-(4-methoxy)-benzoyl derivative **1c** were slightly lower than that of **1b** (Table 4, entries 1–6). The same tendency was also observed with **1e** having a naphtoyl substituent (Table 4, entries 13–15), and even lower selectivity were obtained in these reactions particularly with the bis-alkaloid **(DHQD)$_2$PYR**. Surprising results came from substrate **1d** bearing a nitro substituent on the benzoyl moiety. ee's higher than 60% were achieved for pipecolate **2d** by using *epi*-bases (Table 4, entries 8, 10 and 11) in CCl_4, whereas **CN** and **(DHQD)$_2$PYR** were not able to induce noticeable ee's. The major problem associated with **1d** was its low stability since it underwent partial spontaneous decarboxylation even when stored below 10 °C. This made its preparation difficult and the results were on the selectivities not easy to explain as compared with the other *N*-aroylated substrates.[25] It should be emphasized that the

Table 4. Decarboxylation of **1c–1e** with cinchonine type alkaloids[a]

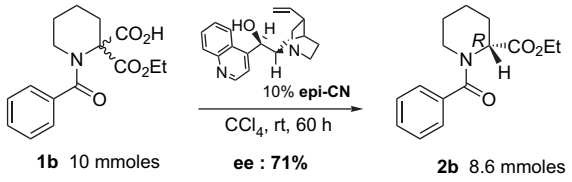
Entry	Starting material R	Base	C_9	ee % (configuration)[c]	
				CCl_4	THF
1		**CN**	*S*	51 (*R*)	48 (*R*)
2		*epi*-**CN**	*R*	*67* (*R*)	*69* (*R*)
3		**CN–*t*-BuCarb**	*S*	41 (*S*)	43 (*S*)
4		**CN–PhCarb**	*S*	9 (*S*)	7 (*S*)
5		*epi*-**CN–Amide**[b]	*R*	36 (*S*)	33 (*S*)
6	**1c**	**(DHQD)$_2$PYR**	*S*	55 (*S*)	35 (*S*)
7		**CN**	*S*	13 (*R*)	11 (*R*)
8		*epi*-**CN**	*R*	*63* (*R*)	20 (*R*)
9		**CN–*t*-BuCarb**	*S*	50 (*S*)	3 (*S*)
10		*epi*-**CN–PhCarb**	*R*	*65* (*S*)	—
11		*epi*-**CN–Amide**[b]	*R*	*67* (*S*)	30 (*S*)
12	**1d**	**(DHQD)$_2$PYR**	*S*	9 (*S*)	—
13		**CN**	*S*	59 (*R*)	45 (*R*)
14		*epi*-**CN**	*R*	47 (*R*)	51 (*R*)
15		**(DHQD)$_2$PYR**	*S*	37 (*S*)	11 (*S*)
	1e				

[a] Reaction conditions: 0.1 mmol of **1b** and 0.1 mmol of the base were left at room temperature for 24 h.
[b] Reactions were carried out for three days.
[c] Absolute configuration of the major enantiomer. ee's were measured by chiral HPLC.

'*epi*' configuration gave better enantioselectivities with equal functional group (**CN** vs *epi*-**CN**, **CN–Amide** vs *epi*-**CN–Amide** and **CN–PhCarb** vs *epi*-**CN–PhCarb**). Improvement of the enantioselectivity was clearly observed for **1d** when replacing THF by CCl_4 (Table 4, entries 8, 9 and 11), whereas no sharp differences were obtained between these solvents with other substrates, for example, the reactions of **1b** with *epi*-**CN** and *epi*-**CN–Amide** (Table 3, entries 8 and 11). However, the best results were generally obtained in carbon tetrachloride.

2.3. Organocatalysis

At this point of the study, our main initial goal was to develop catalytic conditions that could be used on larger amounts of starting material. Preliminary results showed that a substoichiometric amount (50%) of the base was able to promote the asymmetric decarboxylation of our substrate without altering the selectivity (Table 1, entry 7). Hemimalonate **1b** gave consistently the highest ee's with several bases. *epi*-**CN** was also the most efficient base to promote the asymmetric decarboxylation. Having in hands the conditions (base, solvent, substrate) to reach a reasonable control of the enantioselectivity, we demonstrated the possibility of carrying out the reaction under a catalytic amount of chiral base (10%) and on a 10 mmol scale (Scheme 4).



Scheme 4. Preparative organocatalyzed decarboxylation.

The conditions giving the best and most reproducible results (ee: 70–72%) were thus used for the organocatalytic experiment. A mixture of 10 mmol of piperidine **1b** and 10% mol of *epi*-**CN** in CCl_4 stirred at room temperature for 60 h afforded pipecolate **2b** in 86% isolated yield and 71% ee. This result demonstrated that organocatalysis was a well suited methodology for asymmetric decarboxylations and illustrated the potential of this reaction on a more practical scale. This reaction was carried out under very simple and mild conditions. Moreover, the possibility of recovering the catalyst by an acid–base treatment during the work-up is a real plus.

3. Conclusions

The malonic acid synthesis has been largely exploited for the preparation of carboxylic acid derivatives before the advent of selective and powerful methodologies using metal enolates. In its asymmetric organocatalytic version, it was used recently as an alternative route to α-cyano substituted derivatives and linear α-amino acids. The results presented in this work widen the scope of this reaction for the preparation of enantioenriched pipecolic esters derivatives with ee's higher than 70%, which stand as some of the best enantioselectivities obtained for enantioselective decarboxylation. Moreover, the reaction was tested with the same efficiency on a multigram scale. The importance of key parameters on the selectivity, the low polarity of the solvent and the aromatic nature of the nitrogen substituent of the substrate were demonstrated. The temperature was shown to influence only the rate of the decarboxylation and not the enantioselection. A full set of quinidine–cinchonine type of base was prepared. A clear trend showed that the cinchonine analogues (vs quinidine derivatives) were the best catalysts. A steric repulsion between the methoxy group of the quinoline and our substrate was probably occurring with the quinidine family. This study highlighted the little studied effect (compared to other reactions using cinchona alkaloid catalysts) of the configuration at C9 of the base. In general for a given chemical group, the '*epi*' configuration afforded better enantioselectivities and the alcohol group, i.e. *epi*-**CN** is, so far, the best functionality tested. On the asymmetric perspective, this reaction should be viewed as an organocatalyzed enantioselective protonation performed under very simple metal-free conditions, at room temperature and using a catalytic amount of the chiral reagent. Our current efforts are focusing on preparing novel cinchonine derivatives that will provide improved enantioselectivities for the asymmetric decarboxylation of malonyl compounds. Furthermore, this study performed on a model compound, will be generalized to other malonyl derivatives to extend the scope of the methodology.

4. Experimental

4.1. General

Solvents (THF, CH_2Cl_2, MeCN, Et_2O) were dried and purified from Pure-Solv™ 400 Solvent Purification System. CCl_4 was distilled on P_2O_5 and stored over $CaCl_2$. Triethylamine (NEt_3), toluene, $CHCl_3$ and 1,4-dioxane were distilled from CaH_2. All commercially available compounds were used as received. Thin layer chromatography was performed on silica gel 60 F-254 plates (0.1 mm,

Merck) with iodine and/or UV detection. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck). Analytical high performance liquid chromatography (HPLC) was carried out with a Waters instrument [detector M996 (200–400 nm) and pump 600]. All NMR spectra were recorded on a Bruker Avance DPX 250 instrument (250 MHz ^{1}H, 62 MHz ^{13}C) using $CDCl_3$ and TMS as solvent and reference, respectively. Chemical shifts (δ) are given in parts per million and coupling constants (J) in hertz. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. Optical rotations were measured on a Perkin–Elmer 241 LC polarimeter in a 10 cm cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2/g. Analytical data were performed with a Thermoquest NA 2500 instrument. Melting points were determined on a Gallenkamp apparatus and are uncorrected.

4.2. General procedure for the acylation of diethyl aminomalonate (4)

To a stirred solution of diethyl aminomalonate **4** (2.2 g, 10 mmol, 1 equiv) and NEt_3 (4.2 mL, 30 mmol, 3 equiv) in CH_2Cl_2 (150 ml) was added at 0 °C acid chloride (10 mmol, 1 equiv). After stirring 15 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with HCl (1 N) and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

4.2.1. 2-(Benzoylamino)propanedioic acid diethyl ester (3b). Purification of the crude product by recrystallization from AcOEt/heptane (1/10) afforded **3b** as a white solid in 88% yield (2.3 g from 2 g aminomalonate **4**): mp 63 °C; ^{1}H NMR δ 1.32 (t, J=7.1 Hz, 6H), 4.2–4.4 (m, 4H), 5.35 (d, J=7.0 Hz, 1H), 7.10 (br d, J=7.0 Hz, 1H), 7.4–7.5 (m, 3H), 7.8–7.9 (m, 2H); ^{13}C NMR δ 14.1 (CH_3), 56.9 (CH), 62.8 (CH_2), 127.4 (CH), 128.7 (CH), 132.2 (CH), 133.1 (C), 166.5 (C), 166.9 (C); IR (KBr) 3430, 2990, 1740, 1666, 1513, 1022 cm^{-1}; MS (EI) m/z (%) 280 (M$^+$, 3), 262 (2), 234 (8), 207 (12), 189 (9), 161 (14), 105 (100), 77 (25); Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.09; H, 6.28; N, 5.12.

4.2.2. 2-(4-Methoxybenzoylamino)propanedioic acid diethyl ester (3c). Purification of the crude product by flash chromatography on silica gel (CH_2Cl_2/AcOEt, 90/10) afforded amide **3c** as a white solid in 81% yield (7.5 g from 5.4 g aminomalonate **4**): mp 106 °C; ^{1}H NMR δ 1.32 (t, J=7.5 Hz, 6H), 3.85 (s, 3H), 4.2–4.4 (m, 4H), 5.35 (d, J=7.0 Hz, 1H), 6.94 (d, J=8.5 Hz, 2H), 7.05 (br d, J=7.0 Hz, 1H), 7.82 (d, J=8.5 Hz, 2H); ^{13}C NMR δ 14.1 (CH_3), 55.5 (CH_3), 56.9 (CH), 62.7 (CH_2), 113.9 (CH), 125.4 (C), 129.3 (CH), 162.8 (C), 166.3 (C), 166.6 (C); IR (KBr) 3432, 1780, 1662, 1492, 1264 cm^{-1}; MS (EI) m/z (%) 309 (M$^+$, 14), 264 (6), 237 (2), 219 (2), 191 (5), 135 (100), 107 (6), 77 (10); Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.11; H, 6.28; N, 4.59.

4.2.3. 2-(4-Nitrobenzoylamino)propanedioic acid diethyl ester (3d). Purification of the crude product by recrystallization from AcOEt/heptane (1/10) afforded **3d** as a white solid in 62% yield (4.0 g from 5.3 g of aminomalonate **4**): mp 138 °C; ^{1}H NMR δ 1.35 (t, J=7.2 Hz, 6H), 4.2–4.4 (m, 4H), 5.34 (d, J=6.7 Hz, 1H), 7.26 (br d, J=7.2 Hz, 1H), 8.04 (d, J=8.5 Hz, 2H), 8.34 (d, J=8.5 Hz, 2H); ^{13}C NMR δ 14.4 (CH_3), 57.3 (CH), 63.3 (CH_2), 124.2 (CH), 128.9 (CH), 138.9 (C), 150.4 (C), 165.2 (C), 166.4 (C); IR (KBr) 3053, 2985, 1755, 1740, 1677, 1529, 1264 cm^{-1}; MS (EI) m/z (%) 325 (M$^+$, 6), 279 (8), 251 (26), 206 (32), 150 (100), 134 (5), 120 (9), 104 (15), 92 (13); HRMS (EI) calcd for $C_{14}H_{16}N_2O_7$ 325.1036, found 325.1027.

4.2.4. 2-(α-Naphtoylamino)propanedioic acid diethyl ester (3e). Purification of the crude product by recrystallization (CH_2Cl_2/AcOEt: 10/1) afforded **3e** as a white solid in 91% yield (3.0 g from 2.65 g aminomalonate **4**): mp 72 °C; ^{1}H NMR δ 1.35 (t, J=7.0 Hz, 6H), 4.2–4.4 (m, 4H), 5.47 (d, J=7.0 Hz, 1H), 7.04 (br d, J=7.0 Hz, 1H), 7.4–7.6 (m, 3H), 7.73 (d, J=7.2 Hz, 1H), 7.8–8.0 (m, 2H), 8.4 (d, J=8.0 Hz, 1H); ^{13}C NMR δ 14.4 (CH_3), 57.3 (CH), 63.2 (CH_2), 125.0 (CH), 125.7 (CH), 126.1 (CH), 126.9 (CH), 127.7 (CH), 128.7 (CH), 130.6 (C), 131.6 (CH), 133.2 (C), 134.1 (C), 166.9 (C), 169.4 (C); IR (neat) 3266, 2982, 1753, 1737, 1638, 1524, 1349, 1282, 1236, 1157, 781 cm^{-1}; MS (EI) m/z (%) 329 (M$^+$, 27), 284 (7), 237 (7), 211 (3), 155 (100), 127 (29); HRMS (ESI) calcd for $C_{18}H_{20}NO_5$ [M+H]$^+$ 330.1341, found 330.1339.

4.3. Typical procedure for the piperidine ring construction

To a stirred solution of 1,4-dibromobutane (2.5 mL, 21 mmol, 1.05 equiv) and Cs_2CO_3 (15.0 g, 46 mmol, 2.3 equiv) in MeCN (425 mL) was added acylaminomalonic acid diethyl ester (**3**) (20 mmol, 1.0 equiv) in MeCN (20 mL) over 15 h at 70 °C. After 24 h stirring at the same temperature, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (200 mL) was added and the mixture was extracted with CH_2Cl_2 (5×100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

4.3.1. 1-Acetyl-piperidine-2,2-dicarboxylic acid diethyl ester. Purification of the crude product by bulb-to-bulb distillation (200 °C, 0.02 mbar) afforded the title compound (2.25 g from 2.15 g of commercially available starting material **3a**; 84%) as a clear oil; ^{1}H NMR δ 1.29 (t, J=7.0 Hz, 3H), 1.4–1.5 (m, 2H), 1.6–1.7 (m, 2H), 2.03 (s, 3H), 2.2–2.3 (m, 2H), 3.3–3.4 (m, 2H), 4.2–4.3 (m, 4H); ^{13}C NMR δ 14.3 (CH_3), 20.7 (CH_2), 22.6 (CH_3), 24.4 (CH_2), 32.7 (CH_2), 45.4 (CH_2), 62.1 (CH_2), 69.0 (C), 168.6 (C), 173.2 (C); IR (NaCl) 2980, 2944, 2866, 1734, 1668, 1446, 1272 cm^{-1}; MS (EI) m/z (%) 272 (M$^+$+1, 30), 230 (10), 226 (100); HRMS (ESI) calcd for $C_{13}H_{21}NO_5Na$ [M+Na]$^+$ 294.1317, found 294.1320.

4.3.2. 1-Benzoylpiperidine-2,2-dicarboxylic acid diethyl ester. Purification of the crude product by flash chromatography on silica gel (CH_2Cl_2/AcOEt: 97/3) afforded the title compound as a clear oil in 63% yield (6.0 g from 8.0 g of starting material **3b**). ^{1}H NMR δ 1.32 (t, J=7.0 Hz, 6H), 1.60 (br s, 4H), 2.3–2.4 (m, 2H), 3.3–3.4 (m, 2H), 4.2–4.4 (m, 4H), 7.3–7.5 (m, 5H); ^{13}C NMR δ 14.0 (CH_3), 21.0 (CH_2), 24.1 (CH_2), 32.3 (CH_2), 47.0 (CH_2), 61.9 (CH_2), 69.0 (C), 127.0 (CH), 128.4 (CH), 129.9 (CH), 135.7 (C),

168.1 (C), 173.2 (C); IR (NaCl) 3408, 2981, 1733, 1651, 1390, 1230 cm^{-1}; MS (EI) *m/z* (%): 333 (M^+, 6), 260 (71), 228 (5), 105 (100), 77 (24); HRMS (ESI) calcd for $C_{18}H_{24}NO_5$ $[M+H]^+$ 334.1654, found 334.1654.

4.3.3. 1-(4-Methoxybenzoyl)piperidine-2,2-dicarboxylic acid diethyl ester. Purification of the crude product by flash chromatography on silica gel (CH_2Cl_2/AcOEt: 50/50) afforded the title compound as a clear oil in 63% yield (1.5 g from 2 g of starting material **3c**). ^1H NMR δ 1.30 (t, J=7.2 Hz, 6H), 1.61 (br s, 4H), 2.3–2.4 (m, 2H), 3.3–3.4 (m, 2H), 3.83 (s, 3H), 4.2–4.4 (m, 4H), 6.91 (d, J=8.6 Hz, 2H), 7.48 (d, J=8.6 Hz, 2H); ^{13}C NMR δ 14.4 (CH_3), 21.6 (CH_2), 24.7 (CH_2), 32.8 (CH_2), 47.6 (CH_2), 55.8 (CH_3), 62.2 (CH_2), 69.5 (C), 114.2 (CH), 128.2 (C), 129.5 (CH), 161.4 (C), 168.6 (C), 173.5 (C); IR (NaCl) 3447, 2940, 1731, 1576, 1512, 1420, 1003, 840 cm^{-1}; MS (EI) *m/z* (%) 363 (M^+, 4), 318 (5), 290 (35), 228 (4), 135 (100), 107 (6), 92 (4), 77 (10); HRMS (ESI) calcd for $C_{19}H_{26}NO_6$ $[M+H]^+$ 364.1760, found 364.1760.

4.3.4. 1-(4-Nitrobenzoyl)piperidine-2,2-dicarboxylic acid diethyl ester. Purification of the crude product by flash chromatography on silica gel (CH_2Cl_2/AcOEt: 10/0.4) afforded the title compound as a white solid in 60% yield (1.4 g from 2 g of starting material **3d**); mp 128 °C; ^1H NMR δ 1.34 (t, J=7.2 Hz, 6H), 1.5–1.7 (m, 4H), 2.3–2.4 (m, 2H), 3.2–3.3 (m, 2H), 4.2–4.4 (m, 4H), 7.68 (d, J=8.7 Hz, 2H), 8.29 (d, J=8.7 Hz, 2H); ^{13}C NMR δ 14.4 (CH_3), 21.1 (CH_2), 24.3 (CH_2), 32.6 (CH_2), 47.3 (CH_2), 62.5 (CH_2), 69.5 (C), 124.2 (CH), 128.3 (CH), 142.4 (C), 148.8 (C), 168.1 (C), 171.5 (C); IR (KBr) 2950, 2253, 1731, 1654, 1525, 1348, 1230, 912 cm^{-1}; MS (EI) *m/z* (%) 378 (M^+, 4), 333 (4), 305 (100), 259 (5), 150 (52), 120 (6), 104 (9); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_7$ $[M+H]^+$ 379.1505, found 379.1519.

4.3.5. 1-(1-Naphtoyl)piperidine-2,2-dicarboxylic acid diethyl ester. Purification of the crude product by flash chromatography on silica gel (CH_2Cl_2 100% then CH_2Cl_2/AcOEt: 97/3) afforded the title compound as a white solid in 31% yield (0.5 g from 1.4 g of starting material **3e**): mp 105 °C; ^1H NMR δ 1.38 (q, J=7 Hz, 6H), 1.4–1.6 (m, 4H), 2.3–2.5 (m, 2H), 3.1–3.2 (m, 2H), 4.3–4.4 (m, 4H), 7.4–7.6 (m, 4H), 7.8–7.9 (m, 2H), 8.1–8.2 (m, 1H); ^{13}C NMR δ 14.6 (CH_3), 21.2 (CH_2), 24.6 (CH_2), 32.9 (CH_2), 46.7 (CH_2), 62.6 (CH_2), 69.2 (C), 124.4 (CH), 125.5 (CH), 125.6 (CH), 126.9 (CH), 127.5 (CH), 128.6 (CH), 129.7 (CH), 130.1(C), 133.7 (C), 134.5 (C), 168.5 (C), 168.9 (C), 172.9 (C); IR (NaCl) 2982, 2949, 2252, 1732, 1650, 1380, 1237, 910, 740 cm^{-1}; MS (EI) *m/z* (%) 383 (M^+, 11), 337 (10), 310 (39), 236 (6), 155 (100), 127 (24); HRMS (ESI) calcd for $C_{22}H_{25}NO_5$ $[M+Na]^+$ 406.1630, found 406.1637.

4.4. General procedure for preparation of acid

KOH (5–15 equiv) was added to the *N*-protected piperidine-2,2-dicarboxylic acid diester (12.4 mmol) in EtOH (10 mL). The reaction mixture was stirred at room temperature for a time given in each case. Around 70–80% of EtOH were removed under vacuum at a temperature below 20 °C (*caution: in order to avoid degradation, EtOH should not be completely evaporated*). $NaHCO_3$ (aqueous solution, 10%, 50 mL) was added and the aqueous layer was washed with Et_2O (50 mL) then acidified to pH 1 and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and then concentrated at a temperature below 20 °C to give the crude product.

4.4.1. 1-Acetylpiperidine-2,2-dicarboxylic acid monoethyl ester (1a). Saponification: 12 h using 5–7 equiv of KOH. Purification of the crude product by recrystallization from EtOAc/pentane (1/1) afforded **1a** as a white solid in 82% yield (2.03 g from 2.76 g of diester): mp 101–102 °C; ^1H NMR δ 1.29 (t, J=7.0 Hz, 3H), 1.6–1.9 (m, 4H), 2.15 (s, 3H), 2.2–2.3 (m, 1H), 3.6–3.7 (m, 2H), 4.2–4.3 (m, 2H); ^{13}C NMR δ 14.1 (CH_3), 19.3 (CH_2), 22.1 (CH_3), 23.7 (CH_2), 32.2 (CH_2), 44.9 (CH_2), 62.7 (CH_2), 67.3 (C), 170.7 (C), 171.2 (C), 174.3 (C); IR (KBr) 3500, 3052, 2983, 1734, 1652, 1419, 1264 cm^{-1}; MS (EI) *m/z* (%) 199 ($M^+ - CO_2$, 21), 156 (15), 126 (67), 85 (100); Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.32; H, 7.19; N, 5.67.

4.4.2. 1-Benzoylpiperidine-2,2-dicarboxylic acid monoethyl ester (1b). Saponification: 24 h using 12–15 equiv of KOH. Purification of the crude product by recristallization from EtOAc/pentane (1/1) afforded **1b** as a white solid in 60% yield (1.10 g from 2.00 g of diester): mp 106 °C; ^1H NMR δ 1.29 (t, J=7.0 Hz, 3H), 1.8–1.9 (m, 4H), 2.0–2.1 (m, 1H), 2.4–2.5 (m, 1H), 3.4–3.5 (m, 1H), 3.7–3.8 (m, 1H), 4.28 (q, J=7.0 Hz, 2H), 7.4–7.5 (m, 5H); ^{13}C NMR δ 14.0 (CH_3), 19.0 (CH_2), 23.3 (CH_2), 31.46 (CH_2), 46.5 (CH_2), 63.0 (CH_2), 67.6 (C), 127.6 (CH), 128.7 (CH), 131.0 (CH), 134.5 (C), 170.0 (C), 171.2 (C), 175.2 (C); IR (KBr) 3420, 2949, 1734, 1636, 1405, 909, 700 cm^{-1}; MS (ESI) *m/z* (%) 306 (M+1, 50), 288 (26), 260 (100), 232 (7), 216 (9), 156 (69), 105 (26); HRMS (ESI) calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$ 306.1341, found 306.1336.

4.4.3. 1-(4-Methoxybenzoyl)piperidine-2,2-dicarboxylic acid monoethyl ester (1c). Saponification: 24 h using 10 equiv of KOH. Purification of the crude product by recrystallization from EtOAc/pentane (4/6) afforded **1c** as a white solid in 72% yield (1.00 g from 1.50 g starting material): mp 138 °C; ^1H NMR δ 1.27 (t, J=7.5 Hz, 3H), 1.7–1.8 (m, 4H), 2.0–2.1 (m, 1H), 2.4–2.5 (m, 1H), 3.3–3.4 (m, 1H), 3.8–3.9 (m, 1H), 3.85 (s, 3H), 4.2–4.3 (m, 2H), 6.95 (d, J=8.6 Hz, 2H), 7.56 (d, J=8.6 Hz, 2H); ^{13}C NMR δ 14.0 (CH_3), 19.0 (CH_2), 23.4 (CH_2), 31.2 (CH_2), 47.0 (CH_2), 55.4 (CH_3), 62.9 (CH_2), 68.0 (C), 113.8 (CH), 125.8 (C), 130.3 (CH), 162.3 (C), 169.5 (C), 171.0 (C), 176.1 (C); IR (KBr) 3415, 3052, 1606, 1420, 1264, 741 cm^{-1}.

4.4.4. 1-(4-Nitrobenzoyl)piperidine-2,2-dicarboxylic acid monoethyl ester (1d). Saponification: 48 h using 15 equiv of KOH. Progress of the saponification was monitored by ^1H-NMR. Purification of the crude product by recrystallization from EtOAc/pentane (4/6) afforded **1d** as a white solid in 66% yield (800 g from 1.3 g of diester): mp 120 °C; ^1H NMR δ 1.33 (t, J=7.0 Hz, 3H), 1.6–1.8 (m, 4H), 2.2–2.3 (m, 1H), 2.3–2.4 (m, 1H), 3.4–3.5 (m, 2H), 4.35 (m, 2H), 7.6–7.7 (m, 2H), 8.2–8.3 (m, 2H); ^{13}C NMR δ 14.1 (CH_3), 18.9 (CH_2), 23.2 (CH_2), 31.7 (CH_2), 46.2 (CH_2), 63.4 (CH_2), 67.0 (C), 124.2 (CH), 128.3 (CH), 141.1 (C), 149.0 (C), 170.3 (C), 171.6 (C), 172.1 (C); IR (KBr) 3400, 3052, 2883, 1733, 1652, 1525, 1420, 1350, 1264, 750 cm^{-1}; MS

(ESI) *m/z* (%) 351 ([M+H]$^+$, 24), 333 (20), 305 (100) 277 (13.6); HRMS (ESI) calcd for $C_{16}H_{18}N_2O_7$ [M+H]$^+$ 351.1192, found 351.1160.

4.4.5. 1-(1-Naphtoyl)piperidine-2,2-dicarboxylic acid monoethyl ester (1e). Saponification: 24 h using 10 equiv of KOH. Purification of the crude product by recrystallization from EtOAc/pentane (4/6) afforded **1e** as a white solid in 75% yield (400 mg from 580 mg of diester): mp 70 °C; ^{1}H NMR δ 1.3–1.4 (m, 3H), 1.5–1.7 (m, 4H), 2.1–2.2 (m, 1H), 2.3–2.4 (m, 1H), 3.2–3.4 (m, 2H), 4.2–4.5 (m, 2H), 7.3–7.6 (m, 4H), 7.8–7.9 (m, 2H), 8.0–8.2 (m, 1H), 8.2–8.4 (br s, H acid); ^{13}C NMR δ (2 rotamers) 14.4 (CH_3), 18.6 (CH_2), 19.0 (CH_2), 23.2 (CH_2), 23.5 (CH_2), 31.7 (CH_2), 32.0 (CH_2), 45.3 (CH_2), 46.0 (CH_2), 63.7 (CH_2), 66.6 (C), 66.8 (C), 123.6 (CH), 124.3 (CH), 124.9 (CH), 125.2 (CH), 125.4 (CH), 126.5 (CH), 126.7 (CH), 127.1 (CH), 127.5 (CH), 128.1 (CH), 128.5 (CH), 129.4 (C), 129.9 (CH), 132.9 (C), 133.2 (C), 170.0 (C), 170.2 (C), 172.8 (C), 173.0 (C), 173.7 (C); IR (neat) 2944, 1733, 1646, 1375, 1229, 1020, 780; MS (ESI) *m/z* (%) 356 ([M+H]$^+$, 30.1), 338 (8), 310 (28), 155 (100); HRMS (ESI) calcd for $C_{22}H_{21}NO_5$ [M+H]$^+$ 356.1498, found 356.1500.

4.5. Typical decarboxylation procedure

The organic base (0.25 mmol, chiral amine or Et_3N) was added under nitrogen to *N*-protected-piperidine-2,2-dicarboxylic acid monoethyl ester (**1**) (0.25 mmol) in distilled aprotic solvent (10 mL). The mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure (temperature not exceeding 20 °C). After acidification (HCl 1 N), the mixture was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), and then concentrated (temperature not exceeding 20 °C) to give the crude product. Purification was carried out by flash chromatography, and then the enantiomeric excess was determined by HPLC analysis using a Chiralpak AD-H column (250×4.6 mm i.d., 5 μm); mobile phase: 95% of *n*-heptane and 5% of a mixture of MeOH/EtOH: 70/30; flow rate: 1 mL/min; variable temperature and wavelength detection.

4.6. Organocatalyzed decarboxylation of piperidinomalonate hemiester (1b)

epi-Cinchonine (0.3 g, 1.0 mmol) was added under nitrogen to piperidine-2,2-dicarboxylic acid monoethyl ester (**1b**) (3.0 g, 10 mmol) in CCl_4 (10 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed under reduced pressure (temperature not exceeding 20 °C). After acidification (HCl 1 N), the mixture was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), and then concentrated (temperature not exceeding 20 °C) to give the crude product. Purification was carried out by flash chromatography on silica gel to afford **2b** as a colourless oil (2.25 g, 86% yield). The enantiomeric excess was determined by HPLC (ee: 71%).

4.7. General procedure for the synthesis of optically pure pipecolic acid derivatives (HPLC references)

(*S*)-(−)-1-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic acid (229 mg, 1 mmol) was dissolved in a solution of HCl in EtOH (20 mL, 10% v/v) and stirred for 15 h at room temperature. The solvent was evaporated. To the crude product dissolved in a mixture of CH_2Cl_2 (20 mL) and pyridine (2 mL) was added the acid chloride (3 equiv). After 5 h stirring at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with HCl (1 N) and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. After purification on silication gel, the product was subjected to HPLC analysis. All retention times are given for both enantiomers by comparison for the (*R*) enantiomer with the racemic mixtures synthesized by decarboxylation of malonyl derivatives **1** in the presence of Et_3N.

4.7.1. (*S*)-1-Acetylpiperidine-2-carboxylic acid ethyl ester (2a). Purification of the crude product by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 6/4) afforded **2a** as a colourless oil (179 mg, 90% yield): $[\alpha]_D^{20}$ −60 (*c* 5.0, $CHCl_3$); HPLC retention times: (*S*) 11.0 min; (*R*) 8.5 min (*T*: 35 °C, λ: 203 nm); ^{1}H NMR δ (two rotamers a/b: 75/25) 1.27 (t, *J*=6.8 Hz, 3H, a+b), 1.2–1.7 (m, 5H, a+b), 2.07 (s, 3H, b), 2.14 (s, 3H, a), 2.2–2.3 (m, 1H, a+b), 2.6–2.7 (m, 1H, b), 3.30 (dt, *J*=12.4, 2.3 Hz, a), 3.6–3.7 (m, 1H, a), 4.1–4.2 (m, 2H, a+b), 4.4–4.6 (m, 2H, b), 5.3–5.4 (m, 1H, a); ^{13}C NMR δ (two rotamers) 14.5 (a+b, CH_3), 21.0 (b, CH_2), 21.1 (a, CH_2), 21.7 (b, CH_3), 21.9 (a, CH_3), 24.7 (b, CH_2), 25.6 (a, CH_2), 26.9 (a, CH_2), 27.5 (b, CH_2), 39.5 (b, CH_2), 44.4 (a, CH_2), 52.0 (a, CH), 57.2 (b, CH), 61.3 (a, CH_2), 61.8 (b, CH_2), 170.9 (a, C), 171.1 (b, C), 171.6 (a+b, C); IR (NaCl) 2940, 2862, 1735, 1648, 1424, 1200 cm^{-1}; MS (EI) *m/z* (%) 199 (M$^+$, 10), 154 (4), 126 (57), 84 (100); HRMS (EI) calcd. for $C_{10}H_{17}NO_3$ 199.1208, found 199.1202.

4.7.2. (*S*)-1-Benzoylpiperidine-2-carboxylic acid ethyl ester (2b). Purification of the crude product by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 6/4) afforded **2b** as a colourless oil (222 mg, 85% yield). $[\alpha]_D^{20}$ −75 (*c* 0.80, $CHCl_3$); HPLC retention times: (*S*) 14.5 min.; (*R*) 15.4 min; (*T*: 20 °C, λ: 205 nm); ^{1}H NMR δ (two rotamers a/b: 70/30) 1.27 (t, *J*=6.8 Hz, 3H, a+b), 1.3–1.8 (m, 5H, a+b), 2.20 (d, *J*=12.5 Hz, 1H, b), 2.35 (d, *J*=12.5 Hz, 1H, a), 2.83 (t, *J*=12.5 Hz, 1H, b), 3.23 (t, *J*=12.5 Hz, 1H, a), 3.63 (d, *J*=13.5 Hz, 1H, a), 4.2–4.3 (m, 2H, a+b), 4.42 (s, 1H, b), 4.64 (d, *J*=13.5 Hz, 1H, b), 5.49 (d, *J*=4.0 Hz, 1H, a), 7.3–7.5 (m, 5H, a+b); ^{13}C NMR δ (two rotamers) 14.6 (a+b, CH_3), 21.5 (a+b, CH_2), 25.0 (b, CH_2), 25.8 (a, CH_2), 27.0 (a, CH_2), 27.7 (b, CH_2), 40.3 (b, CH_2), 46.2 (a, CH_2), 52.6 (a, CH), 58.8 (b, CH), 61.6 (a, CH_2), 61.9 (b, CH_2), 126.7 (b, CH), 127.2 (a, CH), 128.8 (a, CH), 129.0 (b, CH), 129.9 (a+b, CH), 136.4 (a+b, C), 171.2 (b, C), 171.4 (a, C), 171.9 (a, C), 172.2 (b, C); IR (NaCl) 2939, 2861, 1732, 1633, 1417, 1200, 1139, 1005, 699 cm^{-1}; MS (EI) *m/z* (%) 261 (M$^+$, 11), 216 (2), 188 (100), 156 (5), 105 (100), 77 (27); HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ [M+H]$^+$ 262.1443, found 262.1441.

4.7.3. (*S*)-1-(4-Methoxybenzoyl)piperidine-2-carboxylic acid ethyl ester (2c). Purification of the crude product by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 6/4) afforded **2c** as a colourless oil (200 mg, 69% yield). $[\alpha]_D^{20}$ −65 (*c* 1.0, $CHCl_3$); HPLC retention times: (*S*) 34.0 min; (*R*) 26.0 min (*T*: 35 °C, λ: 240 nm); ^{1}H NMR δ (two rotamers

a/b: 60/40) 1.30 (t, J=7.1 Hz, 3H, a+b), 1.4–1.8 (m, 5H, a+b), 2.1–2.4 (br m, 1H, a+b), 3.7–3.9 (br m, 1H, b), 3.2–3.4 (br m, 1H, a), 3.7–3.8 (br m, 1H, a), 3.83 (s, 3H, a+b), 4.23 (q, J=7.1 Hz, 2H, a+b), 4.5–4.7 (br m, 2H, b), 5.45 (br s, 1H, a), 6. 91 (d, J=8.6 Hz, 2H, a+b), 7.40 (d, J=8.6 Hz, 2H, a+b); ^{13}C NMR δ (2 rotamers) 14.3 (a+b, CH_3), 21.3 (a+b, CH_2), 24.7 (b, CH_2), 25.6 (a, CH_2), 26.8 (a, CH_2), 27.3 (b, CH_2), 40.2 (b, CH_2), 46.1 (a, CH_2), 52.6 (a, CH), 55.4 (a+b, CH_3), 58.8 (b, CH), 61.3 (a+b, CH_2), 113.7 (a+b, C), 127.5 (a+b, CH), 128.0 (a+b, CH), 129.05 (a+b, C), 160.8 (a+b, C), 171.2 (a+b, C), 171.6 (a+b, C); IR (NaCl) 3455, 2940, 2243, 1731, 1632, 1512, 1422, 1003, 912, 840, 728 cm^{-1}; MS (EI) m/z (%) 291 (M^+, 9), 218 (34), 135 (100), 107 (5); HRMS (ESI) calcd for $C_{16}H_{21}NO_4$ $[M+H]^+$ 292.1549, found 292.1540.

4.7.4. (*S*)-1-(4-Nitrobenzoyl)piperidine-2-carboxylic acid ethyl ester (2d). Purification of the crude product by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 6/4) afforded **2d** as a colourless oil (260 mg, 85% yield). $[\alpha]_D^{20}$ −60 (c 0.45, $CHCl_3$); HPLC retention times: (*S*) 23.5 min; (*R*) 31.0 min; (*T*: 35 °C, λ: 262 nm); ^{1}H NMR δ (2 rotamers a/b: 75/25) 1.33 (t, J=7.1 Hz, 3H, a+b), 1.3–1.8 (m, 5H, a+b), 2.23 (d, J=13.2 Hz, 1H, b), 2.39 (d, J=13.2 Hz, 1H, a), 2.86 (t, J=12.9 Hz, 1H, b), 3.29 (t, J=12.9 Hz, 1H, a), 3.47 (d, J=12.9 Hz, 1H, a), 4.2–4.3 (m, 2H, a+b, and 1H, b), 4.65 (br d, J=13.9 Hz, 1H, b), 5.47 (d, J=4.8 Hz, 1H, a), 7.5–7.6 (m, 2H, a+b), 8.2–8.3 (m, 2H, a+b); ^{13}C NMR δ (two rotamers) 14.7 (a+b, CH_3), 21.4 (a+b, CH_2), 24.9 (b, CH_2), 25.7 (a, CH_2), 26.9 (a, CH_2), 27.6 (b, CH_2), 40.5 (b, CH_2), 46.2 (a, CH_2), 52.8 (a, CH), 58.7 (b, CH), 61.9 (a, CH_2), 62.3 (b, CH_2), 124.3 (a, CH), 124.4 (b, CH), 127.9 (b, CH), 128.3 (a, CH), 142.6 (a+b, C), 148.7 (a+b, C), 169.7 (a+b, C), 171.0 (a+b, C); IR (NaCl) 3445, 2933, 1734, 1640, 1522, 1430, 1347, 1173, 1021, 852 cm^{-1}; MS (EI) m/z (%) 306 (6), 233 (100), 150 (42), 120 (5), 104 (9); HRMS (ESI) calcd for $C_{15}H_{19}N_2O_5$ $[M+H]^+$ 307.1294, found 307.1278.

4.7.5. 1-(1-Naphtoyl)piperidine-2-carboxylic acid ethyl ester (2e). Purification of the crude product by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 6/4) afforded **2e** as a colourless oil (245 mg, 79% yield). $[\alpha]_D^{20}$ −94 (c 1.3, $CHCl_3$); HPLC retention times: (*S*) 9.0 min; (*R*) 13.7 min; (*T*: 20 °C, λ: in nm); ^{1}H NMR δ (four rotamers a/b/c/d in approximate ratio: 51/24/15/10, respectively) 1.16, 1.28, 1.38, 1.43 (d, c, b, a, respectively) (t, J=7.1 Hz, 3H), 1.3–1.8 (m, 5H, a+b+c+d), 2.0–2.1 (m, 1H, c+d), 2.4–2.5 (m, 1H, a+b), 2.97 (td, J=13.4 and 3.2 Hz, 1H, c), 3.0–3.2 (m, 1H, a+b+d), 3.3–3.4 (m, 1H, a+b), 4.0–4.1 (m, 2H, d), 4.12 (br d, J=5.0 Hz, 1H, d), 4.2–4.4 (m, 2H, a+b+d and 1H, c), 4.8–4.9 (m, 1H, c+d), 5.73 (d, J=5.0 Hz, 1H, a+b), 7.4–7.6 (m, 4H, a+b+c+d), 7.8–7.9 (m, 2.5H), 8.13 (d, J=8.1 Hz, 0.5H); ^{13}C NMR δ (four rotamers a, b, c, d) 14.4 (d, CH_3), 14.6 (c, CH_3), 14.7 (b, CH_3), 14.8 (a, CH_3), 21.5–21.6 (a+b+c+d, CH_2), 25.3 (d, CH_2), 25.4 (c, CH_2), 25.8 (a, CH_2), 26.2 (b, CH_2), 27.1 (a, CH_2), 27.2 (b, CH_2), 27.8 (d, CH_2), 28.2 (c, CH_2), 39.3 (d, CH_2), 40.0 (c, CH_2), 45.6 (a, CH_2), 46.0 (b, CH_2), 52.4 (a+b, CH), 58.4 (c, CH), 58.5 (d, CH), 61.8–61.9 (a+b+c+d, CH_2), 123.5, 123.8, 124.1, 124.3, 124.6, 124.8, 125.0, 125.3, 125.6, 125.7, 125.8, 126.1, 126.3, 126.8, 126.9, 127.3, 127.4, 127.5, 128.5, 128.6, 128.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 129.9, 130.1, 130.2, 133.7, 133.8, 134.1, 134.46, 134.4, 134.5, 134.7, 134.8 (aromatic carbons of rotamers a, b, c, d), 170.8–171.0–171.1 (a+b+c+d, C), 171.2 (b, C), 171.3 (d, C), 171.4 (c, C), 171.5 (a, C); IR (NaCl) 3442, 3016, 1731, 1628, 1437, 1215, 756; MS (EI) m/z (%) 311 (20), 265 (5), 238 (50), 155 (100), 127 (28); HRMS (ESI) calcd for $C_{19}H_{21}NO_3$ $[M+H]^+$ 312.1600, found 312.1597.

4.8. Synthesis of cinchona alkaloid derivatives

4.8.1. *N*-(9-Deoxycinchonin-9-yl)-2-methoxybenzamide—CN–Amide. To (8*R*, 9*S*)-9-amino-(9-deoxy)-cinchonine (0.530 g, 1.83 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (1.62 mL, 11.52 mmol) and DMAP (0.032 g, 0.26 mmol). The mixture was cooled to 0 °C and *o*-anisoyl chloride (0.641 g, 3.76 mmol) in CH_2Cl_2 (10 mL) was added. Stirring was continued at 0 °C for 30 min then at room temperature for three days. After addition of NaOH (2 N, 10 mL), the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography over silica gel (CH_2Cl_2/MeOH: 95/5) afforded **CN–Amide** (0.703 g, 90%) as a white solid: mp 88–89 °C; $[\alpha]_D^{20}$ +13.2 (c 0.26, EtOH); ^{1}H NMR δ 1.5–1.8 (m, 4H), 1.8–2.0 (m, 1H), 2.1–2.3 (m, 1H), 2.6–2.9 (m, 4H), 3.4–3.5 (m, 1H), 3.86 (s, 3H), 4.9–5.1 (m, 2H), 5.9–6.1 (m, 1H), 6.2–6.3 (m, 1H), 6.93 (d, J=8.4 Hz, 1H), 7.0–7.1 (m, 1H), 7.3–7.5 (m, 2H), 7.5–7.6 (m, 1H), 7.6–7.7 (m, 1H), 8.0–8.2 (m, 2H), 8.30 (d, J=8.5 Hz, 1H), 8.38 (d, J=8.5 Hz, 1H), 8.90 (d, J=4.6 Hz, 1H); ^{13}C NMR δ 25.4 (CH_2), 26.6 (CH_2), 28.2 (CH), 40.3 (CH), 48.4 (CH_2), 49.4 (CH_2), 50.2 (CH), 56.1 (CH_3), 59.4 (CH) 111.4 (CH), 114.9 (CH_2), 118.7 (CH), 121.2 (C), 121.5 (CH), 123.8 (CH), 126.9 (CH), 127.4 (C), 129.2 (CH), 130.3 (CH), 132.5 (CH), 133.1 (CH), 140.4 (CH), 148.0 (C), 148.9 (C), 150.1 (CH), 157.4 (C), 165.0 (C); IR (KBr) 3482, 3357, 2938, 1600, 1541, 1243, 1023, 756 cm^{-1}; MS (EI) m/z (%) 427 (M^+, 48), 386 (10), 332 (16), 292 (88), 135 (100), 77 (27); HRMS (ESI) calcd for $C_{27}H_{30}N_3O_2$ $[M+H]^+$ 428.2338, found 428.2334.

4.8.2. Cinchonin-9-yl phenylcarbamate—CN–PhCarb. Phenyl isocyanate (1.44 g, 12.10 mmol) was added to a solution of cinchonine (2.73 g, 9.26 mmol) in toluene (30 mL). The reaction mixture was heated at 110 °C for 16 h. Toluene was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH: 97.5/2.5) to afford **CN–PhCarb** (2.88 g, 75%) as a white solid: mp 201–202 °C [lit.[13] 190–191 °C]; $[\alpha]_D^{20}$ +51 (c 0.8, $CHCl_3$) [lit.[13] +53 (c 0.54, $CHCl_3$)]; ^{1}H NMR δ 1.4–1.6 (m, 2H), 1.8–2.0 (m, 2H), 2.25 (q, J=8.2 Hz, 1H), 2.6–2.8 (m, 2H), 2.90 (d, J=8.9 Hz, 2H), 3.34 (q, J=8.5 Hz, 1H), 5.0–5.2 (m, 2H), 5.9–6.1 (m, 1H), 6.57 (d, J=7.9 Hz, 1H), 6.79 (br s, 1H), 7.06 (t, J=7.1 Hz, 1H), 7.2–7.4 (m, 5H), 7.44 (d, J=4.5 Hz, 1H), 7.5–7.6 (m, 1H), 7.6–7.7 (m, 1H), 8.13 (d, J=8.3 Hz, 1H), 8.25 (d, J=8.4 Hz, 1H), 8.90 (d, J=4.5 Hz, 1H); ^{13}C NMR δ 24.4 (CH_2), 26.4 (CH_2), 27.8 (CH), 39.8 (CH), 49.0 (CH_2), 49.7 (CH_2), 59.9 (CH), 74.0 (CH), 115.1 (CH_2), 119.1 (CH), 119.2 (CH) 123.8(CH), 123.9 (CH), 126.6 (C), 127.1 (CH), 129.2 (CH), 129.4 (CH), 130.4 (CH), 138.0 (C), 140.6 (CH), 146.3 (C), 148.6 (C), 150.0 (CH), 153.0 (C); IR (KBr) 3240, 3064, 2938, 1730, 1600, 1545, 1445, 1317, 1219, 1053, 758 cm^{-1}; MS (ESI) m/z (%) 414 (M+1, 17), 295 (3), 277 (100), 246 (2), 234 (4);

HRMS (ESI) calcd for $C_{26}H_{28}N_3O_2$ $[M+H]^+$ 414.2182, found 414.2162.

4.8.3. Cinchonin-9-yl *tert*-butylcarbamate—CN–*t*-BuCarb. Tertiobutyl isocyanate (1.20 g, 12.10 mmol) and one drop of dibutyltin laurate were added to cinchonine (2.73 g, 9.26 mmol) in toluene (30 mL). The reaction mixture was heated at 110 °C for 48 h. Toluene was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel (acetone) to afford **CN–*t*-BuCarb** (3.60 g, 99%) as a white solid: mp 115–116 °C; $[\alpha]_D^{20}$ +71 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.28 (s, 9H), 1.4–1.6 (m, 2H), 1.8–2.0 (m, 2H), 2.1–2.3 (m, 1H), 2.6–2.9 (m, 5H), 3.2–3.3 (m, 1H), 4.76 (br s, 1H), 5.0–5.2 (m, 2H), 5.9–6.1 (m, 1H), 6.48 (d, *J*=7.1 Hz, 1H), 7.39 (d, *J*=4.5 Hz, 1H), 7.57 (td, *J*=7.4, 1.1 Hz, 1H), 7.70 (td, *J*=7.4, 1.2 Hz, 1H), 8.11 (d, *J*=8.3 Hz, 1H), 8.22 (d, *J*=8.2 Hz, 1H), 8.88 (d, *J*=4.5 Hz, 1H); ^{13}C NMR δ 24.1 (CH_2), 26.4 (CH_2), 27.8 (CH), 28.8 (CH_3), 39.8 (CH), 48.9 (CH_2), 49.7 (C), 50.6 (CH_2), 59.8 (CH), 72.9 (CH), 114.6 (CH_2), 118.4 (CH), 123.6 (CH), 126.2 (C), 126.7 (CH), 129.0 (CH), 130.2 (CH), 140.6 (CH), 146.3 (C), 148.4 (C), 149.9 (CH), 153.7 (C); IR (neat) 3278, 2952, 1723, 1506, 1262, 1202 1098, 1049, 770 cm^{-1}; MS (ESI) *m/z* (%) 394 (M^++1, 45), 295 (14), 277 (100), 234 (3); HRMS (ESI) calcd for $C_{24}H_{32}N_3O_2$ $[M+H]^+$ 394.2495, found 394.2482.

4.8.4. *epi*-Cinchonin-9-yl phenylcarbamate—*epi*-CN–PhCarb. Phenyl isocyanate (1.052 g, 8.83 mmol) was added to *epi*-cinchonine (2 g, 6.79 mmol) in toluene (22 mL). The reaction mixture was heated at 110 °C for 5 h. Toluene was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH: 97.5/2.5) to afford *epi*-**CN–PhCarb** (2.53 g, 90%) as a white solid: mp 108 °C; $[\alpha]_D^{20}$ +115.4 (*c* 0.58, $CHCl_3$); ^{1}H NMR δ 0.9–1.0 (m, 1H), 1.1–1.3 (m, 1H), 1.7–1.4 (m, 3H), 2.1–2.3 (m, 1H), 2.7–3.0 (m, 3H), 3.1–3.3 (m, 1H), 3.50–3.67 (m, 1H), 5.0–5.2 (m, 2H), 5.75–5.95 (m, 1H), 6.69 (d, *J*=10.21 Hz, 1H), 6.93 (t, *J*=7.0 Hz, 1H), 7.05–7.27 (m, 4H), 7.58 (d, *J*=4.4 Hz, 1H), 7.66 (t, *J*=7.3 Hz, 1H), 7.78 (t, *J*=7.3 Hz, 1H), 8.19 (d, *J*=8.2 Hz, 1H), 8.52 (d, *J*=8.3 Hz, 1H), 8.59 (br s, 1H), 8.99 (d, *J*=4.4 Hz, 1H); ^{13}C NMR δ 24.2 (CH_2), 26.1 (CH_2), 27.2 (CH), 39.0 (CH), 47.4 (CH_2), 48.6 (CH_2), 59.6 (CH), 71.6 (CH), 115.0 (CH_2), 119.3 (CH), 120.0 (CH), 123.3 (CH), 123.7 (CH), 126.8 (C), 127.1 (CH), 128.6 (CH), 129.6 (CH), 130.4 (CH), 138.0 (C), 139.8 (CH), 144.1 (C), 148.7 (C), 149.9 (CH), 153.5 (C); IR (neat) 3241, 3062, 2938, 1725, 1601, 1544, 1314, 1222, 1054, 758 cm^{-1}; MS (ESI) *m/z* (%) 414 (M+1, 12), 295 (3), 277 (100), 234 (4); Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.39; H, 6.94; N, 10.16.

4.8.5. 4,6-bis(Cinchonin)-2,5-diphenylpyrimidine—$(CN)_2$PYR. A mixture of 4,6-dichloro-2,5-diphenylpyrimidine (301 mg, 1 mmol), cinchonine (589 mg, 2 mmol) and KOH (560 mg, 10 mmol) in toluene (30 mL) was stirred at room temperature for 10 min then at 115 °C for 15 h with azeotropic removal of water. After cooling to room temperature, water was added and the aqueous layer was extracted ($CHCl_3$). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (EtOAc/MeOH: 98.5/1.5) to afford **$(CN)_2$PYR** (534 mg, 65%) as a white solid: mp 115–116 °C; $[\alpha]_D^{20}$ –127.5 (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 1.1–1.7 (m, 8H), 1.7–1.9 (t, *J*=11.0 Hz, 2H), 2.0–2.2 (m, 2H), 2.5–2.9 (m, 8H), 3.0–3.2 (m, 2H), 4.7–5.0 (m, 4H), 5.2–5.4 (m, 2H), 6.7–7.9 (m, 18H), 8.14 (d, *J*=8.3 Hz, 2H), 8.29 (d, *J*=8.3 Hz, 2H), 8.87 (d, *J*=4.3 Hz, 2H); ^{13}C NMR δ 22.7 (CH_2), 26.3 (CH_2), 28.4 (CH), 40.5 (CH), 49.8 (CH_2), 49.9 (CH_2), 60.0 (CH), 76.8 (CH), 104.7 (C), 114.7 (CH_2), 118.2 (CH), 123.6 (CH), 126.0 (C), 126.6 (CH), 127.7 (CH), 128.6 (CH), 129.1 (CH), 130.4 (CH), 130.5 (CH), 131.2 (C), 136.3 (C), 140.4 (CH), 146.9 (C), 148.5 (C), 150.0 (CH), 161.0 (C), 166.3 (C); IR (KBr) 3064, 2936, 2869, 1578, 1539, 1414, 1361, 1110 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{53}N_6O_2$ $(M+H)^+$ 817.4230, found 817.4223.

Acknowledgements

We gratefully acknowledge the 'Ministère de la Recherche et des Nouvelles Technologies' for fellowships T.S., 'PunchOrga' Network (Pôle Universitaire Normand de Chimie Organique), CNRS (Centre National de la Recherche Scientifique), the 'Région Basse-Normandie', and the European Union (FEDER funding) for financial support.

References and notes

1. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.
2. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Application in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
3. (a) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195–205; (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497; (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
4. Martin, J.; Deagostino, A.; Perrio, C.; Dauphin, F.; Ducandas, C.; Morin, C.; Desbène, P.-L.; Lasne, M.-C. *Bioorg. Med. Chem.* **2000**, *8*, 591–601.
5. Martin, J.; Lasne, M.-C.; Plaquevent, J.-C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181–7182.
6. Martin, J. Ph.D. Dissertation, University of Caen-Basse Normandie, 1998.
7. (a) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349; (b) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1368.
8. (a) Kenyon, J.; Ross, W. A. *J. Chem. Soc.* **1952**, 2307; (b) Asperger, R. G.; Liu, C. F. *Inorg. Chem.* **1967**, *6*, 796–800; (c) Verbit, L.; Halbert, T. R.; Patterson, R. B. *J. Org. Chem.* **1975**, *40*, 1649–1650.
9. (a) Job, R. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 809–819; (b) Glusker, J. P.; Carrell, H. L.; Job, R.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 5741–5751; (c) Ajioka, M.; Yano, S.; Matsuda, K.; Yoshikawa, S. *J. Am. Chem. Soc.* **1981**, *103*, 2459–2460; (d) Yamaguchi, M.; Yamamatsu, S.; Oikawa, H.; Saburi, M.; Yoshikawa, S. *Inorg. Chem.* **1981**, *20*, 3179–3186; (e) Yashiro, M.; Ajioka, M.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Inorg. Chem.* **1986**, *25*, 1709–1715.
10. Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1987**, *28*, 539–542.
11. Darensbourg, D. J.; Holtcamp, M. W.; Khandelwal, B.; Klausmeyer, K. K.; Reibenspies, J. H. *Inorg. Chem.* **1995**, *34*, 2389–2398.

12. Brunner, H.; Müller, J.; Spitzer, J. *Monatsh. Chem.* **1996**, *127*, 845–858.
13. Hénin, F.; Muzart, J.; Nedjma, M.; Rau, H. *Monatsh. Chem.* **1997**, *128*, 1181–1188.
14. (a) Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119–2133; (b) Brunner, H.; Baur, M. A. *Eur. J. Org. Chem.* **2003**, 2854–2862.
15. (a) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755–2761; (b) Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2002**, 3986–3994; (c) Roy, O.; Dieckmann, M.; Riahi, A.; Hénin, F.; Muzart, J. *Chem. Commun.* **2001**, 533–534; (d) Aboulhoda, S. J.; Reiners, I.; Wilken, J.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1847–1850; (e) Muzart, J.; Hénin, F.; Aboulhoda, S. J. *Tetrahedron: Asymmetry* **1997**, *8*, 381–389; (f) Aboulhoda, S. J.; Hénin, F.; Muzart, J.; Thorey, C.; Behnen, W.; Martens, J.; Mehler, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1321–1326.
16. (a) Miyamoto, K.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 4077–4078; (b) Matoishi, K.; Hanzawa, H.; Suzuki, M.; Sugai, T.; Ohta, H. *Chem. Commun.* **2000**, 1519–1520; (c) Matoishi, K.; Ueda, M.; Miyamoto, K.; Ohta, H. *J. Mol. Catal., B Enzym.* **2004**, *27*, 161–168; (d) Ijima, Y.; Matoishi, K.; Terao, Y.; Doi, N.; Yanagawa, H.; Ohta, H. *Chem. Commun.* **2005**, 877–879.
17. Miyamoto, K.; Ohta, H. *Biocatalysis* **1991**, *5*, 49–60.
18. (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566–2587; (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653–3691.
19. Rogers, L. M.-A.; Rouden, J.; Lecomte, L.; Lasne, M.-C. *Tetrahedron Lett.* **2003**, *44*, 3047–3050.
20. For recent examples of organocatalytic reaction affording best selectivities in nonpolar solvents, see: (a) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167–169; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
21. (a) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154–3155; (b) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870–2871.
22. For the data of the acetyl derivative **3a**, see Ref. 19.
23. (a) Maier, N. M.; Nicoletti, L.; Lämmerhofer, M.; Lindner, W. *Chirality* **1999**, *11*, 522–528; (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.
24. We noticed a lack of reproducibility of certain results: as an example we could not reproduce the enantiomeric excess of 52% obtained with the base **QD–Amide** in THF, see Ref. 19.
25. For compound **2d**, we checked for the asymmetric deprotonation–reprotonation according to the conditions described for **2b** at the end of Section 2.1. Again, no such effect was observed for this product.