

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,*}

^aLaboratoire de Chimie Moléculaire et Thio-organique, UMR CNRS 6507—ENSICAEN, Université de Caen-Basse Normandie,
 6 Boulevard du Maréchal Juin, 14050 Caen Cedex, France

^bIRCOF, 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 piperidinoheimalonates catalyzed by cinchona alkaloids. Enantiomeric excesses as high as 72% were obtained when using 9-*epi*-cinchonine and the *N*-benzoyl substituted piperidinoheimalonate. 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.

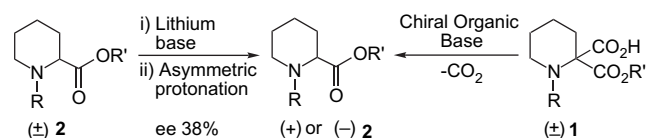
© 2006 Elsevier Ltd. All rights reserved.

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 M₂ 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 dera-cemization 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 -aminomalononic 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 group¹² and then Hénin–Muzart¹³ proved that copper was not necessary, thus developing the first organocatalytic asymmetric decarboxylations.

Keywords: Organocatalysis; Enantioselective decarboxylation; Pipecolate; Cinchona alkaloids.

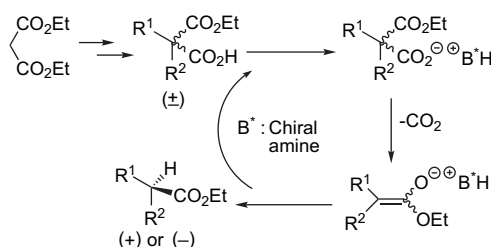
* Corresponding author. Tel.: +33 131452893; fax: +33 131452877; e-mail: jacques.rouden@ensicaen.fr

Then, Brunner studied the decarboxylation of an α -cyano-carboxylic 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 debenzyla-tion–decarboxylation.¹⁵ Finally, a decarboxylase, isolated from a bacterium strain, was shown to catalyze the enantio-selective decarboxylation of arylalkylmalonic acids with ee's up to 97%.¹⁶ The main drawback of these reagents re-mains their high degree of specificity for the substrate.¹⁷

In this paper we described our extensive work on the asym-metric decarboxylation of malonyl pipercolates **1** catalyzed by cinchona alkaloids to synthesize enantiomerically en-riched pipercolate ester **2** (Scheme 1). The selectivity of the reaction was studied as a function of different reaction pa-rameters (solvent, concentration, temperature), of the sub-strate (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 depro-tonation 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

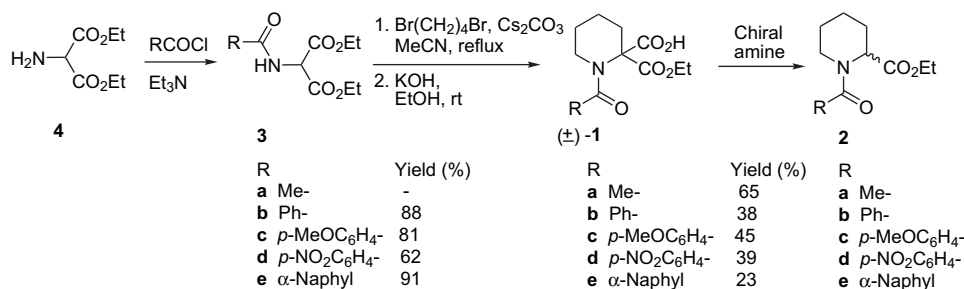
carboxylate loses carbon dioxide affording an intermediate enolate, which should be rapidly protonated to generate an enantiomerically enriched α -substituted ester. On the asym-metric point of view, the chirality of the product is introduced at the final step and the whole process resembles the enantio-selective 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 irre-versible 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 decar-boxylation under simple and mild conditions to generate **2a**. Several chiral amines were screened and cinchona alka-loids were the most efficient bases to induce asymmetry.¹⁹ The study of the different reaction parameters on the enantio-selectivity was undertaken with **1b**, easily detected by HPLC, and prepared in a three-step sequence starting from amino-malonate **4** (Scheme 3).

The optically pure pipercolates **2** were prepared independ-ently and fully characterized in order to determine the enantiomeric excess and absolute configuration of the enan-tiomers formed in asymmetric decarboxylations. In our first experiments, the reactions were conducted in THF, the sol-vent of choice for the decarboxylations.¹⁴ A quick survey of the four commercially available cinchona alkaloids re-vealed that cinchonine (CN), used in a 1/1 ratio with **1b**, in-duced 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 con-centration 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 temper-ature 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



Scheme 3. Synthesis of substrates.

Download English Version:

<https://daneshyari.com/en/article/5226112>

Download Persian Version:

<https://daneshyari.com/article/5226112>

[Daneshyari.com](https://daneshyari.com)