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Enantioselective Catalysis XXIII [1]. Aminoalcohol Assisted Decarboxylation of 2-Carboxy-2-methyl-1-tetralone leading to Enantioenriched 2-Methyl-1-tetralone

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Summary. Catalytic amounts of enantiopure aminoalcohols assist the decarboxylation of 2-carboxy-2-methyl-1-tetralone to 2-methyl-1-tetralone affording enantiomeric excesses of up to 35%. A rapid screening of the efficiency of various potential inductors of enantioselectivity has been carried out using circular dichroism spectroscopy.

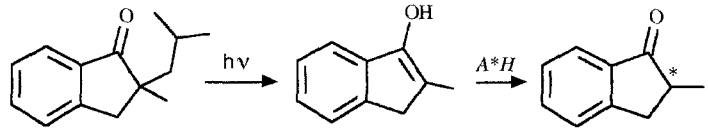
Keywords. Decarboxylation; Enantioselectivity; Catalysis; β-Ketoacid; Aminoalcohol; Circular dichroism.

Enantioselektive Katalyse, 23. Mitt. [1]. Bildung von optisch angereichertem 2-Methyl-1-tetralon durch aminoalkoholunterstützte Decarboxylierung von 2-Carboxy-2-methyl-1-tetralon

Zusammenfassung. Katalytische Mengen von enantiomerenreinen Aminoalkoholen beschleunigen die Decarboxylierung von 2-Carboxy-2-methyl-1-tetralon. Es werden Enantiomerenüberschüsse von bis zu 35% erzielt. CD-Spektroskopie erlaubt eine schnelle Abschätzung der Effizienz von Aminoalkoholen und anderen Verbindungen als Katalysatoren für asymmetrische Reaktionen.

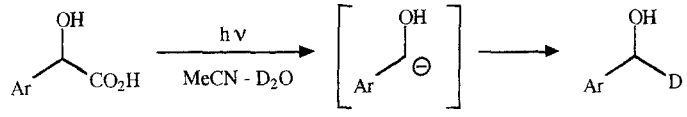
Introduction

In 1991, we reported on the enantioselective formation of 2-methyl-1-indanone by photochemical irradiation of 2-methyl-2-isobutyl-1-indanone in the presence of catalytic amounts of enantiopure aminoalcohols (*A*H*) [2]. This involved a *Norrish* type II reaction leading to 2-methyl-3-indenol whose tautomerization was assisted by *A*H* (Eq. 1). This process has then been extended to various 1-indanone and 1-tetralone derivatives [3].



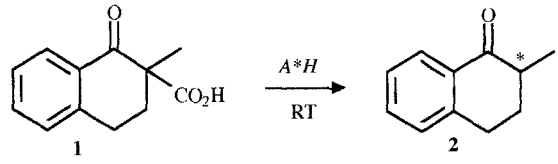
(1)

At the same time, the photochemistry of α-hydroxyarylacetic acids in aqueous media was reported [4]. These compounds photodecarboxylate *via* α-hydroxyarylmethyl carbanions to afford the corresponding arylmethanols (Eq. 2). This prompted us to examine the photoreactivity of 2-carboxy-2-methyl-1-tetralone (**1**) in the presence of enantiopure protic species [5]. We expected to obtain the enolate of 2-methyl-1-tetralone and then non-racemic 2-methyl-1-tetralone (**2**).



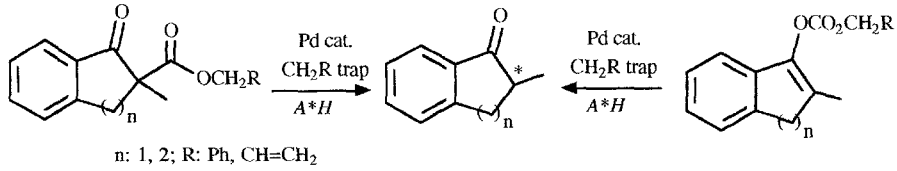
(2)

In the course of this study, we also examined the possibility to induce the enantioselective decarboxylation of **1** by copper(I) salts and *A*H* as described by *Toussaint et al.* for phenylmalonic acids and their hemiesters [6]*. We observed that the enantioselective decarboxylation of **1** to **2** is effective in the presence of enantiopure aminoalcohols without requiring assistance by UV light or copper [5, 8] (Eq. 3).



(3)

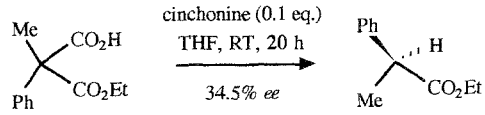
Subsequently, we became involved in a project dealing with the formation of optically active ketones from ketoesters and enol carbonates by a palladium induced cascade reaction [1, 9, 10] (Scheme 1) in which a decarboxylation step was important, too.



Scheme 1

* See also a subsequent study of *Brunner*'s group [7].

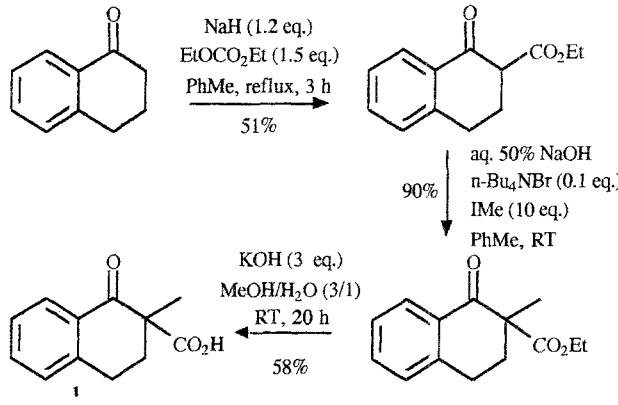
The recent paper of *Brunner et al.* concerning the decarboxylation of malonic acids [11] has revitalized our interest in the decarboxylation of **1**. *Brunner*'s paper demonstrates that – in contrary to previous reports – *i*) the enantioselective decarboxylation of the monoethyl ester of methylphenylmalonic acid is effective when using cinchona alkaloids without other additives (Eq. 4) and *ii*) when present, the role of copper(I) compounds was not that of catalysts but of bases. *Brunner*'s study urges us to communicate our results.



(4)

Results and Discussion

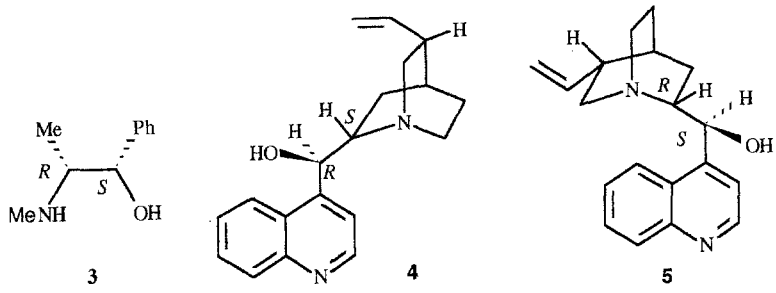
Ketoacid **1** was synthesized from 1-tetralone as shown in Scheme 2 [12, 13]. **1** is sensitive to hydrolytic influences and was thus easily decarboxylated to **2**. The low stability of β-ketoacids has been already documented elsewhere [14, 15].



Scheme 2

Decarboxylation under irradiation

Irradiation of deoxygenated acetonitrile solutions of **1** containing stoichiometric amounts or excesses of enantiopure protic species were carried out in circular dichroism (CD) cells with a nitrogen laser ($\lambda = 337$ nm) for a few minutes at room temperature. The presence of (1*S*,2*R*)-ephedrine (**3**) and cinchonidine (**4**) led to the appearance of the same negative CD signals at $\lambda \geq 300$ nm, the main one being centered at 329 nm. Analysis of the irradiated solutions by TLC indicated the formation of **2**. In contrast, the original CD spectrum of the mixture was not modified with time when (*R*)-α-methylbenzylamine or (*R*,*R*)-O-dipivaloyltartaric acid were used as the protic species.



3 4 5

Following these observations, preparative experiments have been carried out at 0°C in acetonitrile. After irradiation for 25 min, (*S*)-**2** was isolated in 75–80% yield, the enantiomeric excess (*ee*) being 20 and 30% with 0.55 and 1.1 eq. of **3** respectively, and 30% with 1.1 eq. of **4**.

Decarboxylation in the presence of Cu(I) without irradiation

After a few experiments, we have observed that the *ee*s obtained from decarboxylations in the presence of Cu(I)/*A*H*, were more reproducible if **1** was added to a prestirred mixture of the copper salt and aminoalcohol in acetonitrile. Thus, the *ee* of (*S*)-**2** was 17% with Cu_2O (2 eq.)/**4** (0.55 eq.), 5% with Cu_2O (0.2 eq.)/**3** (0.5 eq.), and 8% with CuCl (0.2 eq.)/**4** (0.4 eq.).

Decarboxylation in the dark without Cu(I)

In the presence of 1.3 eq. of **3**, similar results were obtained with and without irradiation. Furthermore, we observed that the CD signals at $\lambda \geq 300$ nm increased during 1.5 h after mixing **1** and ephedrine. We have already mentioned that CD spectroscopy is a very useful method for a rapid and confident screening of enantioselective reactions under various conditions [16]. Therefore, the decarboxylation of **1** in the dark was examined at room temperature in acetonitrile in the presence of various protic species (1–1.3 eq.). Negative CD signals similar to those discussed above were observed with (1*S*,2*S*)-pseudoephedrine, **4**, and brucine. The corresponding opposite CD signals – *i.e.*, positive with the main band centered at 329 nm – appeared with (1*R*,2*S*)-O-methylephedrine, (1*R*,2*S*)-N-methylephedrine, (1*S*,2*R*)-norephedrine, (1*R*,2*S*)-2-(N-isopropylamino)-1-phenyl-1-propanol, and cinchonine (**5**). However, the signals observed with O-methylephedrine, N-methylephedrine, 2-(N-isopropylamino)-1-phenyl-1-propanol, and brucine were weak or very weak. No new signal was observed with (*S*)-proline, sparteine, or sparteine bisulfate. Figure 1 shows a few selected results.

From a comparison of CD spectra obtained using **3**, it can be seen that similar *ee* values were found in chloroform instead of acetonitrile, whereas the use of hexane as solvent decreased greatly the *ee*. As exemplified in Fig. 2, we also observed that the rate of appearance of the CD signal – *i.e.*, the rate of the whole reaction – was higher with **3** than with norephedrine.

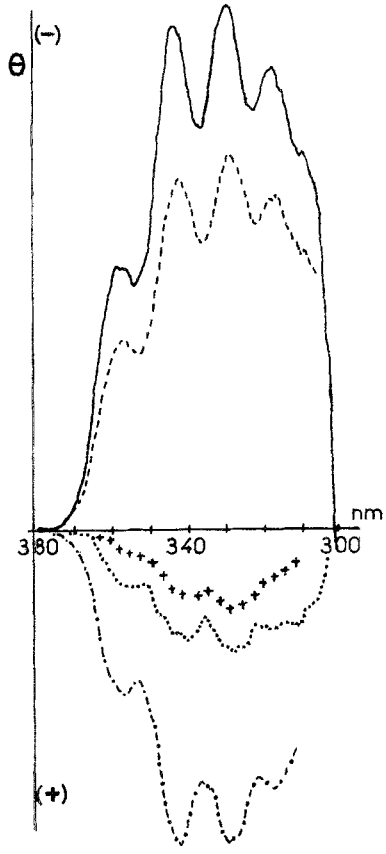


Fig. 1. CD spectra from reaction mixtures of **1** and various aminoalcohols recorded after complete decarboxylation of **1** (stirring for 2–5 h); (1*S*,2*R*)-ephedrine: —, (1*S*,2*S*)-pseudoephedrine: - - - -, (1*R*,2*S*)-2-(N-isopropylamino)-1-phenyl-1-propanol: ++, (1*R*,2*S*)-N-methylephedrine:· · ·, (1*S*,2*R*)-norephedrine:— · —·

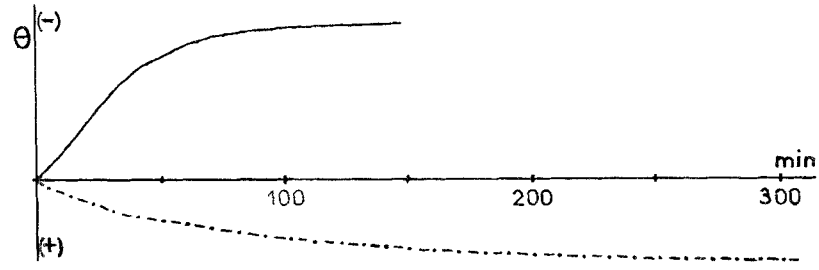


Fig. 2. Time evolution of the CD spectra of a mixture of **1** and either (1*S*,2*R*)-ephedrine (—) or (1*S*,2*R*)-norephedrine (— · —·) at $\lambda = 329$ nm

Finally, preparative experiments were carried out by slow addition of **1** to a stirred solution of 0.2 eq. of either **3** or **5** in acetonitrile at room temperature. Thus, **2** was isolated in 70–74% yield and 30–35% *ee*, the main enantiomer being *S* from **3** and *R* from **5**. These rather moderate *ee*s nevertheless indicate that more than one mole of enantiomerically pure **2** is produced per mole of **3** or **4**.

Conclusions

The decarboxylation of racemic β-ketoacids assisted by catalytic amounts of enantiopure aminoalcohols can lead to the corresponding optically active ketones. This reaction does not require catalysis by copper(I) compounds or irradiation. These results are in agreement with those of *Brunner et al.* and extend the concept of enantioselective decarboxylation of hemiesters by basic non-racemic species [11] to α,α-disubstituted β-ketoacids.

Experimental

Materials and general procedures

Acetonitrile was distilled successively over P_2O_5 and CaH_2 before use. Chiral reagents were commercial except (1*R*,2*S*)-O-methylephedrine [17], (1*R*,2*S*)-N-methylephedrine [18], and (1*R*,2*S*)-2-(N-isopropylamino)-1-phenyl-1-propanol [19] which were prepared by literature procedures. (*R*,*R*)-O-dipivaloyltartaric acid was kindly supplied by Dr. *L. Duhamel.* IR spectra were obtained in chlorofom using a SP 3000-Philips IR spectrometer. ^{1}H NMR spectra were recorded in deuterated chloroform on a CW 80 Bruker NMR spectrometer employing tetramethylsilane as internal reference. Enantiomeric excesses and absolute configurations were determined using a 241-Perkin Elmer polarimeter and comparing the obtained optical rotations with literature data [20]. CD spectra were recorded using an 1 cm round cell and a JASCO-500 spectropolarimeter with a microprocessor. Irradiations were performed at 337 nm using deoxygenated solutions and a Lambda Physik nitrogen pulse laser (600 kW) at a repetition frequency of about 50 s^{-1}.

2-Carboethoxy-1-tetralone

1-Tetralone (1 g) was added dropwise to a stirred mixture of NaH (60% dispersion in oil, 326 mg) and diethyl carbonate (1.2 g) in toluene (16 ml) under an argon atmosphere. The mixture was heated to reflux for 3 h to give a paste which was cooled to room temperature and acidified with 2 *M* hydrochloric acid. Extraction was carried out with diethyl ether. The organic extracts were washed with brine and then dried over magnesium sulfate. After evaporation of the solvents under reduced pressure, 2-carboethoxy-1-tetralone (727 mg) was isolated by flash chromatography [21] eluting with EtOAc/petroleum ether (5/95). The spectroscopic data were in agreement with those given in the literature [22].

2-Carboethoxy-2-methyl-1-tetralone

A 50% sodium hydroxide solution in water (11.5 ml) was added slowly to a solution of 2-carboethoxy-1-tetralone (1 g) in toluene (55 ml) at room temperature. After vigorous high-speed stirring for 3 h, three portions of tetrabutylammonium bromide (50 mg each) were added at intervals of 30 min. Then, three portions of methyl iodide (1 ml each) were added at intervals of 1 h. The stirring was continued for 6 h. Extraction and chromatography as above led to 2-carboethoxy-2-methyl-1-tetralone (960 mg); the spectroscopic data of which were in agreement with those given in the literature [22].

2-Carboxy-2-methyl-1-tetralone

A mixture of potassium hydroxide (362 mg) and 2-carboethoxy-2-methyl-1-tetralone (477 mg) in water-methanol (1/3, 14 ml) was stirred for 20 h at room temperature. Water and dichloromethane

were added. The aqueous phase was recovered, acidified with 2 *M* hydrochloric acid, and extracted with dichloromethane. The organic extract was dried and evaporated to dryness to afford 2-carboxy-2-methyl-1-tetralone (242 mg).

IR: $\nu = 3000$ (wide), 1710, 1680, 1595, 1455, 1305 cm^{-1}; ^1H NMR: $\delta = 10.65$ (1H), 8.05 (m, 1H), 7.4 (m, 3H), 3.0 (m, 2H), 2.55 (m, 1H), 2.1 (m, 1H), 1.5 (s, 3H) ppm.

Decarboxylation under irradiation

Nitrogen was bubbled for 5 min into a 10 cm cell containing **1** (27.4 mg), cinchonidine (43 mg), acetonitrile (15 ml), and a magnetic stirrer bar. The cell was placed in an ice-cooled water bath, and the mixture was irradiated for 25 min under stirring. The mixture was stirred for 3 h more and then evaporated to dryness under reduced pressure. Flash chromatography of the residue eluting with EtOAc/hexane (10/90) led to **2** (18.6 mg). The optical rotation of this sample ($[\alpha]_D^{21} = -15$ ($c = 3.7$, CH_2Cl_2)) was compared with the literature value of (*S*)-2-methyl-1-tetralone: $[\alpha]_D^{22} = -51.2$ ($c = 2.5$, dioxane) [20]*.

Decarboxylation in the presence of Cu(I) without irradiation

A solution of **1** (10 mg) in MeCN (15 ml) was added dropwise during 18 h to a stirred mixture of copper oxide (14 mg) and cinchonidine (8 mg) in MeCN (10 ml). The mixture was evaporated to dryness and flash chromatographed to give **2** (4.1 mg), $[\alpha]_D^{21} = -9$ ($c = 0.82$, CH_2Cl_2).

Decarboxylation in the dark without Cu(I)

To a stirred solution of (1*S*,2*R*)-ephedrine (3.6 mg) in MeCN (10 ml), a solution of **1** (10 mg) in MeCN (15 ml) was added dropwise at room temperature (addition time: 12 h). The mixture was stirred for further 10 h. Evaporation of the solvent an flash chromatograhy of the residue led to **2** (5.5 mg), $[\alpha]_D^{21} = -17$ ($c = 1.1$, CH_2Cl_2).

Acknowledgements

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* We observed that the optical rotation of **2** has the same value in both CH_2Cl_2 and dioxane.

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