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Enantioselective Decarboxylation of β-Keto Esters with Pd/Amino Alcohol Systems: Successive Metal Catalysis and Organocatalysis

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Abstract: The kinetics and mechanisms of one-pot cascade reactions of racemic β-keto esters to give chiral ketones in the presence of Pd/C-chiral amino alcohol catalyst systems were studied. Transformation of 2-methyl-1-tetralone-2-carboxylic acid benzyl ester (**1**) into 2-methyl-1-tetralone (**4**) in the presence of Pd/C and cinchona alkaloids or ephedrine was chosen as a model reaction. After the first reaction step, the Pd-catalysed debenzylation of **1** to afford the corresponding β-keto acid (**2**), there are two possible reaction routes that may be catalysed by the chiral amino alcohol in solution or by Pd^0 sites on the metal surface in cooperation with the adsorbed amino alcohol. The reaction intermediate **2** was synthesized, and the kinetics of decarboxylation were followed by NMR, UV and IR spectroscopy. The studies revealed that the role of Pd is to trigger the reaction series by deprotection of **1**. The subsequent dominant reaction route from the racemic β-keto acid **2** to the chiral ketone **4** is catalysed by the chiral amino alcohol in the liquid phase. It is shown that kinetic resolution of the diastereomeric salt of *rac*-**2** and the chiral amino alcohol plays a key role in the enantioselection. High enantioselectivity necessitates an amino alcohol/*rac*-**2** ratio of at least 2. A high ratio favours the formation of 1:1 amino alcohol/acid diastereomeric complexes, and the second amino alcohol molecule may be responsible for the enantioselective protonation of **2** in the diastereomeric complex.

Keywords: β-keto esters · alkaloids · asymmetric catalysis · kinetic resolution · palladium

Introduction

In the field of heterogeneous enantioselective catalysis, most efforts have been focused on hydrogenation reactions,[1–6] whereas other reaction types such as the Pd-catalysed enol isomerization (cascade reaction) have attracted only limited interest. In the field of homogeneous catalysis, however, enantioselective protonation of achiral enolates or enol equivalents, as is applied in the synthesis of chiral building blocks for generation of tertiary carbon stereocentres, has been extensively studied during the past few years.[7–23] The Pd-induced one-pot cascade reactions of racemic α-disubstituted benzyl β-keto esters or enol carbonates to the corresponding chiral ketones represent an alternative method to the asymmetric protonation of enolates.[23–34] This cascade (domino) reaction, extensively studied by Muzart and Hénin, is usually performed in the presence of a supported Pd catalyst and a chiral 1,2-amino alcohol. The catalyst system allows the efficient synthesis of linear and cyclic ketones[26,28,29,31] such as indanones, tetralones and chromanones.[24,25,30] The reaction cascade shown in Scheme 1 represents a typical example including deprotection (debenzylation), decarboxylation and asymmetric protonation as key steps.[25–27] The deprotection reaction catalysed by metallic Pd provides an acid or a carboxylate **2**, which reacts further by decarboxylation to provide an enol or enolate **3**. Asymmetric protonation of the enolate, assisted by a chiral amino alcohol, gives the final ketone **4**. The enantioselectivities are usually in the 60–80% range, with only a few exceptions.[32] Only a small amount of a chiral amino alcohol (0.1–0.3 equiv) is required to provide a chiral product when starting from a benzyl β-keto ester,[26,35] and so the reaction was assumed to be catalytic.[24–27,35] Similarly, only catalytic amounts of amino alcohols are required for the enantiose-

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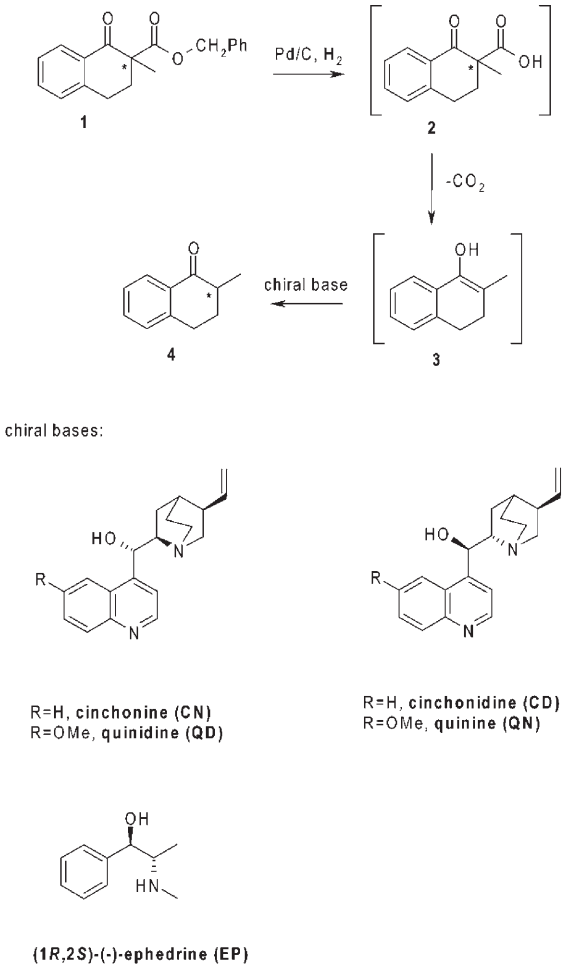
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: Synthesis of starting materials and their characterization, as well as the characterization of intermediates and products and additional details regarding UV/Vis and ATR-IR spectroscopy measurements.



Scheme 1. Domino reaction of **1** to give **4**, together with the structures of chiral amino alcohols.

lective protonation of enol intermediates formed by photochemical irradiation of α-disubstituted ketones.[35–37]

The first enantioselective decarboxylation reaction was reported in 1904 by Marckwald.[38,39] Decarboxylation of malonic acid derivatives with copper salts and cinchona alkaloids was studied,[40–42] but it was shown later that the reaction is not copper- but base-catalysed.[43–45] Enantioselective decarboxylation has been applied for the preparation of α-amino acids,[46,47] Naproxen derivatives[48,49] and various derivatives of β-hydroxyisobutyric acid.[11] These reactions are carried out in homogeneous phase, in the absence of any metal catalyst. The amount of chiral base used in the reaction varies in the 10–100 mol% range and the enantioselectivities are not remarkably high.

There are only a few available mechanistic studies on the Pd-catalysed enantioselective decarboxylation–protonation reactions.[25–27,30,33] In the example of the reaction series in Scheme 1, (supported) Pd^0 is the catalyst for deprotection of the ester. The subsequent steps may be catalysed by the chiral amino alcohol ("inductor") in the homogeneous phase, or the reaction series may proceed on the Pd surface with the assistance of the chiral base. The latter possibility is supported by the frequent observation that the characteristics of the supported Pd have a major influence on the reaction rate and enantioselectivity.[28–30] Decarboxylation on metallic Pd occurs even at room temperature,[50] but for preparative purposes the reaction is usually carried out at 100–300 °C.[51,52] In addition, formally the enantioselective protonation is similar to enantioselective hydrogenations over Pd modified by strongly adsorbing chiral compounds, such as cinchona alkaloids. These reactions occur at the metal surface and the chiral information is transferred by the substrate–modifier interaction during hydrogen uptake.[2,53,54]

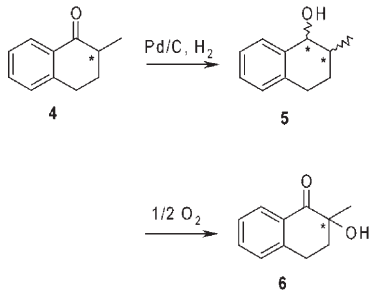
The aim of this study was to investigate the different steps of the Pd^0/amino alcohol catalysed enantioselective decarboxylation–protonation reaction and to clarify the roles of the catalyst components in the reaction mechanism. Our recent study of the structural effects in the Pd-induced cascade reactions of α,α-disubstituted β-keto esters in the presence of a broad range of chiral amines and amino alcohols provided some hints as to the subordinate role of Pd in the enantioselection.[55] Here we report kinetic and spectroscopic studies using the transformation of **1** into **4** in the presence of ephedrine and the four major cinchona alkaloids as chiral bases in a frequently used test reaction (Scheme 1).[27,28,31,32,35]

Results and Discussion

General features of the domino reaction: We first analysed the influence of some key reaction parameters on the overall reaction rate and enantioselectivity in the transformation of *rac*-**1** into **4**. Five different alkaloids (1,2-amino alcohols) were tested in combination with a Pd/C catalyst (Table 1). It has been shown that amino alcohols afford far better enantioselectivities than amines, although the absolute configuration of the ketone product depends on the configuration of the carbon carrying the amino group, not the OH group.[31] Before addition of the substrate, the catalyst was carefully prereduced in situ in the reactor to transform the surface oxides into metallic Pd, thus to obtain reproducible kinetic data. The chemoselectivity in favour of **4** was always better than 90%; the dominant by-products were 2-methyl-1-tetralol (**5**) and 2-hydroxy-2-methyl-1-tetralone (**6**), probably formed from **4** (Scheme 2). Both by-products were isolated and characterized by GC-MS and NMR (see Supporting Information). The amount of **5** increased with longer reaction times and with higher pressure and temperature, while the

Table 1. Enantioselective domino reaction of **1** to give **4**.

Amino alcohol	Conversion [%]	Yield [%]	*ee* [%]
(−)-ephedrine (EP)	100	91	20 (*R*)
(−)-cinchonidine (CD)	76	97	21 (*S*)
(+)-cinchonine (CN)	99	93	22 (*R*)
(−)-quinine (QN)	88	96	59 (*S*)
(+)-quinidine (QD)	92	94	58 (*R*)



Scheme 2. Major by-products formed during the domino reaction of **1** to give **4**.

amount of **6** increased when the catalyst was not pre-reduced or when the reaction was carried out in the presence of air.

The highest enantioselectivities were achieved with QN and QD, alkaloids that—unlike CN and CD—possess methoxy-substituted isoquinoline rings.[55] For further experiments, QN was chosen as the model amino alcohol.

The influence of the amino alcohol to substrate ratio on the reaction rate and enantioselectivity is illustrated in Figure 1. The *ee* increased rapidly with increasing QN/**1** molar ratio up to 0.3–0.5, while the effect above this ratio was negligible. This correlation indicates that a relatively high concentration of amino alcohol is required for the enantioselective step. An inverse correlation in the reaction rate was observed. (Note that the conversion was determined by GC and HPLC; later on only conversions based on calibrated GC results were used.) The negative effect of the alkaloid on the level of conversion is probably due to strong adsorption of the alkaloid on the Pd surface, leading to fewer free active sites being available for the adsorption and hydrogenolysis of the substrate. For purposes of comparison, quinoline is a well known poison of metal hydrogenation catalysts,[56] and addition of cinchona alkaloids to Pd retards the enantioselective hydrogenation of various unsaturated compounds.[57–62]

Variation of the Pd to substrate ratio revealed that on decreasing the amount of Pd the conversion of **1** decreased, as expected, but that the enantioselectivity in **4** remained unaffected (see Supporting Information).

In order to obtain deeper insight into the reaction mechanism, the kinetics of the whole reaction series were studied. A typical course of the cascade reaction of **1** at two different temperatures is depicted in Figure 2. The reaction proceeds significantly more rapidly at higher temperature, but the enantioselectivity is slightly lower.

A new observation is that the enantioselectivity at low levels of conversion is higher than the final value. The observed change is more significant at lower temperature. The probable explanation for the conversion-dependent enantioselectivity is that the QN/**2** ratio varies with conversion: with increasing conversion the ratio decreases as more and more **2** is formed. At high levels of conversion the ratio increases again in parallel with the consumption of **2**, but the

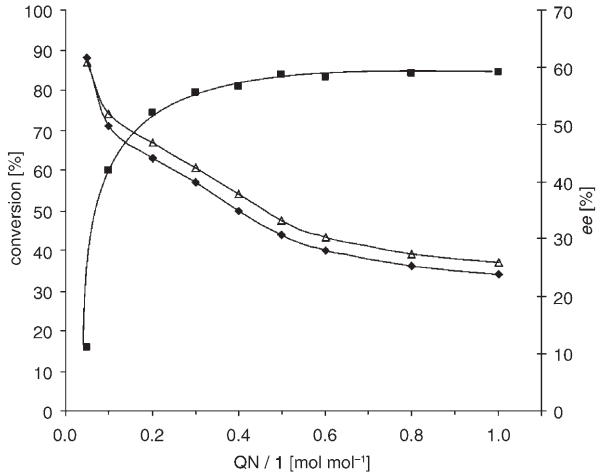


Figure 1. Influence of the QN/**1** molar ratio on the conversion of **1** (GC: △, HPLC: ◆) and the enantioselectivity (■) of **4**. Conditions: **1** (20 mg), Pd/C (5 wt%, 3.6 mg), QN (0.05–1.0 equiv), acetonitrile (2 mL), H_2 (1 bar), 90 min, RT.

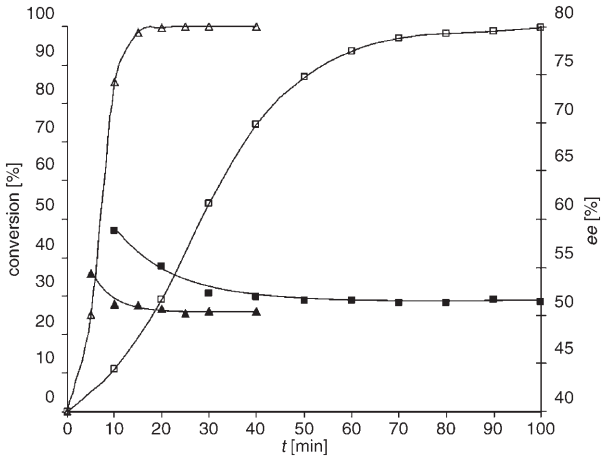


Figure 2. Variation of enantioselectivity (35 °C: ■, 55 °C: ▲) and conversion (35 °C: □, 55 °C: △) as a function of reaction time and temperature. Conditions: **1** (100 mg), QN (33 mg, 0.3 equiv), acetonitrile (10 mL), Pd/C (5 wt%, 18 mg), H_2 (1 bar).

resulting higher actual (incremental) *ee* may not be seen, as only the overall (integral) *ee* can be measured. In order to validate this assumption and to gain a closer look at the reaction mechanism, the intermediate *rac*-**2** was synthesized and its decarboxylation was investigated separately from the debenzylation step.

Organocatalysis in the decarboxylation of *rac*-2: Decarboxylation of **2** in the absence of Pd/C was studied at various QN to acid ratios (Figure 3). The stability of the β-keto acid **2** was reasonably high under the conditions applied, and the rate of the uncatalysed reaction was negligibly low. We found that high acid concentrations and the use of polar protic solvents accelerated the decarboxylation (not shown). Addition of the chiral base enhanced the reaction rate remarkably up to equimolar amino alcohol/acid ratios; the

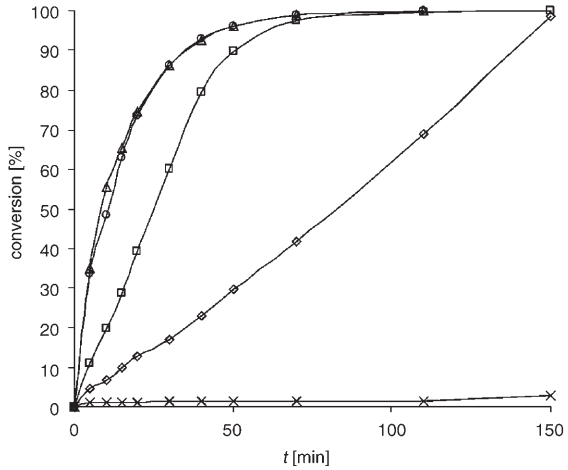


Figure 3. Influence of the QN to **2** molar ratio (0–2 equiv QN) on the rate (conversion) of the decarboxylation of **2** in the absence of Pd/C. Conditions: **2** (40 mg), QN (0 (×), 0.1 (◇), 0.3 (□), 1 (△) and 2 equiv (○)), acetonitrile (5 mL), stirring under argon.

rates in the presence of 1 or 2 equivalents base were practically identical. The unusual rate acceleration with increasing conversion at 0.1 QN/acid molar ratio is attributed to the increasing actual QN/acid ratio with increasing conversion of the acid.

To clarify the role of Pd in the decarboxylation reaction, the experiments in Figure 3 were repeated in the presence of 0.05 equivalent of Pd. Figure 4 illustrates the changes at two different QN/**2** molar ratios. Clearly, the rate of the decarboxylation step in the cascade reaction was diminished by addition of Pd/C, independently of the QN/**2** ratio. The enantioselectivity in the formation of **4** was barely influenced by the presence of Pd, as is discussed later. A feasible explanation for the rate deceleration induced by the addition of Pd/C is the strong adsorption of QN on the Pd surface through its quinoline ring (for comparison, see the ATR-IR study of the adsorption of CD on Pd).[63] As a result, the concentration of free QN in solution decreases and the decarboxylation of **2** becomes slower. If Pd were involved in the reaction mechanism, then the reaction rate should increase and the enantioselectivity should be shifted by the addition of Pd/C. We propose that decarboxylation of the keto acid intermediate is catalysed by the chiral amino alcohol and that the only role of Pd is to "trigger" the cascade reaction by deprotection of **1** to afford *rac*-**2** (Scheme 1).

Another indication of organocatalysis is the observation that at least two equivalents of chiral amino alcohol are required to achieve high enantioselectivity in the decarboxylation of **2** (Figure 5). With increasing QN to acid molar ratio the enantioselectivity increased remarkably and flattened out only when more than two equivalents of the chiral base were used. This correlation confirms our assumption that a high amino alcohol/acid ratio is required for the enantioselective step. In the cascade reaction from **1** to **4** it is sufficient to introduce 0.3–0.5 equivalents of QN relative to the substrate **1** because the intermediate acid **2** is produced gradually on the Pd surface, so the actual QN/**2** ratio is always kept at high level. A feasible explanation for the necessity of a high QN/**2** ratio is that two molecules of the chiral amino alcohol probably interact with one molecule of the acid **2** during the decarboxylation reaction. One equivalent of the amino alcohol reacts with the acid to form a diastereomeric salt, and the second equivalent probably assists the enantioselective step. In this respect it is interesting that the correlation between the QN/**2** molar ratio and the *ee* is influenced by the solvent (Figure 5). We speculate that the correlation observed in CH_2Cl_2 is "distorted" in acetonitrile due to its interaction as a base (H-bond acceptor) with the diastereomeric complex.

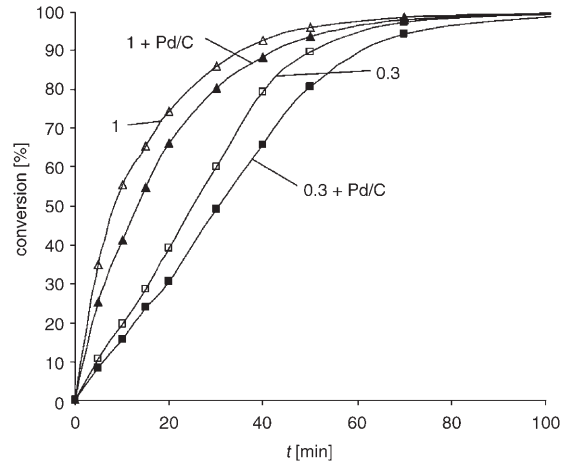


Figure 4. Effect of the addition of Pd/C on the rate of the decarboxylation of **2** at two different QN/**2** molar ratios (0.3 and 1 equiv). Conditions: **2** (40 mg), QN (0.3 and 1 equiv), Pd/C (5 wt%, 20 mg), acetonitrile (5 mL), stirring under argon.

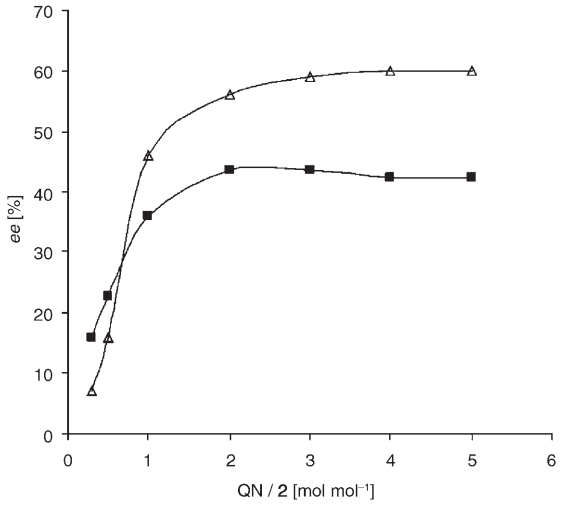


Figure 5. Influence of QN to **2** molar ratio and the solvent on enantioselectivity. Conditions: **2** (40 mg), solvent (5 mL), stirring under argon for 70 min, CH_2Cl_2: △, acetonitrile: ■.

Kinetic resolution in the decarboxylation of 2: Variation of the enantioselectivity with time in the transformation of **2** is illustrated in Figure 6. The enantioselectivities measured at 100% conversion correspond to the values obtained in the experiments shown in Figure 5. In the experiments carried out with QN (1.0 and 2.0 equivalents) the enantioselectivity increased with reaction time until full conversion of **2**. On the other hand, in the presence of only 0.3 equivalent of QN a complex initial transient period is seen: the *ee* drops at the beginning of the reaction (at conversions below 10%) and then it increases again to a final, stable value. A closer look at the data revealed that the missing initial decay at high QN/2 ratios was probably due to the much higher reaction rate.

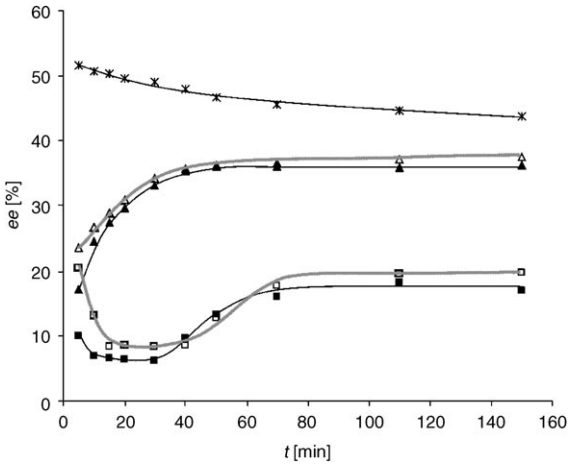


Figure 6. Development of *ee* during decarboxylation of the acid **2** and the effect of the presence of Pd/C on enantioselectivity: △: QN (1 equiv), no Pd/C; ▲ QN (1 equiv) with Pd (0.05 equiv); □: QN (0.3 equiv), no Pd/C; ■: QN (0.3 equiv) with Pd (0.05 equiv); *: QN (0.3 equiv), continuous addition of the acid **2**. Conditions: **2** (40 mg), QN (0.3 and 1 equiv), Pd/C (5 wt%, 20 mg), acetonitrile (5 mL), stirring under argon.

We thus repeated the experiments with a focus on the initial part of the reaction, and we have plotted the enantioselectivities as a function of conversion in Figure 7. In this presentation of the data, the development of enantioselectivity with conversion is qualitatively similar for all experiments, but the lower the QN/**2** ratio, the bigger is the drop in *ee* at low levels of conversion.

The decrease in enantioselectivity in the early stages of the reaction is presumably the result of a kinetic resolution. One of the two diastereomeric salts formed between the racemic **2** and QN probably reacts more rapidly than the other diastereomer, and so a product containing a higher amount of one enantiomer of **4** is produced preferentially at low levels of conversion. This effect is later compensated as the other less reactive diastereomer reacts as well, and the drop in *ee* occurs only at low levels of conversion. The increase in *ee* at higher levels of conversion is explained by the increasing actual QN to acid ratio due to consumption

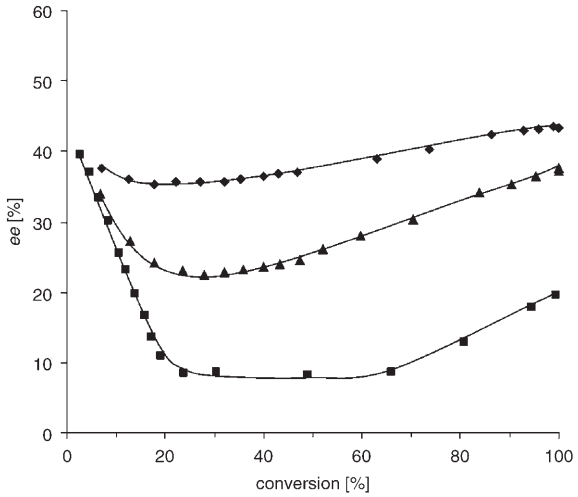


Figure 7. Development of *ee* with conversion during decarboxylation of the acid **2**. The minima in *ee* at 0.3 (■), 1 (▲) and 2 equiv (◆) QN were reached at 15, 5 and 3 min reaction time, respectively. Conditions: **2** (40 mg), QN (0.3, 1 and 2 equiv), acetonitrile (5 mL), stirring under argon.

of the latter. In support of this interpretation, the influence of conversion on the variation of the calculated actual QN/**2** ratio is shown in Figure 8. In the cases of 1.0 and 2.0 equivalents of alkaloid (initial values), the actual ratios are already increasing significantly at low levels of conversion, while when only 0.1 and 0.3 equivalent alkaloid are employed, the actual QN/**2** ratio increases strongly only at above 70% conversion.

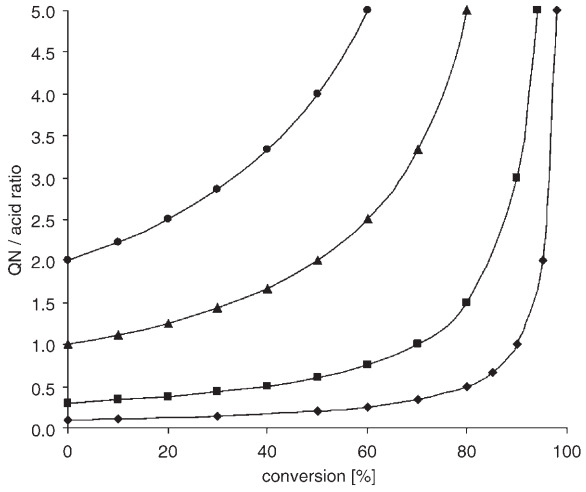


Figure 8. Calculated dependence of QN to acid **2** molar ratio on the conversion of **2** as a function of the initial QN/2 ratio, 0.1 (◆), 0.3 (■), 1 (▲) and 2 equiv (●).

To simulate the cascade reaction of **1** to give **4**, we repeated the decarboxylation of **2** in the presence of QN (0.3 equiv, relative to the total amount of **2**) and fed the acid continuously into the solution of acetonitrile and QN. The high *ee* persisted during the whole reaction and it decreased only slightly with time (Figure 6). During the continuous ad-

dition of the acid, the QN to acid molar ratio decreased monotonously, this shift diminishing the enantioselectivity as expected. Note also the negligible effect of the addition of Pd/C on the enantioselectivity. This observation is in line with our proposal that the Pd surface does not play a role in the enantioselective transformation of **2**. Its role is to provide *rac*-**2** at a slow rate to maintain the high chiral base/**2** ratio in solution and thus to allow high enantioselectivity in the amino alcohol catalysed enantioselective decarboxylation.

The interaction between the chiral amino alcohol and **2** was investigated by NMR. The acid undergoes a slow spontaneous decarboxylation at room temperature (see Figure 3), and the NMR measurements were therefore carried out at −10 °C. This temperature was sufficiently low to prevent the decarboxylation of the acid. Addition of one equivalent of the amino alcohol to **2** resulted in the formation of two diastereomeric species: the salts of the acid and the chiral amino alcohol at a molar ratio of 1:1. The diastereomers differ in their ^{1}H and ^{13}C chemical shifts; almost all signals of the acid are doubled (see Supporting Information). A part of the 1H NMR spectrum of EP and **2** is shown in Figure 9.

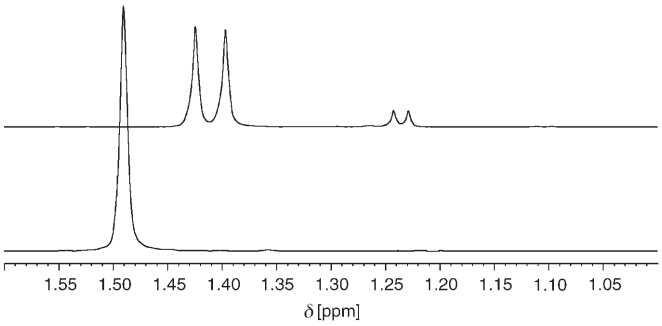


Figure 9. NMR analysis of the interaction of the acid **2** with one equivalent ephedrine (EP) in CD_2Cl_2. Bottom: pure acid ($c = 1\,mol\,L^{-1}$) at −10 °C. Top: diastereomeric salt at 0 °C.

The singlet at 1.49 ppm, which belongs to Me-C(2) of the acid, splits into two signals at 1.40 and 1.43 ppm immediately after addition of the amino alcohol. The chemical shifts and the distance of the signals depend on, among other factors, the temperature of the measurement. At lower temperature, the signals appeared at lower chemical shifts and vice versa. Several 2D-NMR experiments including COSY and NOE were carried out (at −10 °C) in order to determine the structures of the diastereomeric salts, but no significant intermolecular interaction could be observed with 1 or 2 equivalents of QN or EP.

After the temperature had been increased to 30 °C, one of the diastereomers started to disappear from the reaction mixture more rapidly and the chiral ketone **4** was formed. The diastereomers decarboxylated at different rates until almost full conversion. The rate of decarboxylation was followed through the proton signals of the methyl group at C(2) in the acid **2** and the product **4** (Figure 10). During the reaction the signal of the diastereomeric carboxylate appearing at a lower chemical shift (1.43 ppm, measured at 30 °C) decreased more rapidly then the other one (1.46 ppm), while the signal of the methyl group at C(2) of ketone **4**, represented by a doublet at 1.26 ppm, increased continuously (Figure 10). The proton signals were integrated, and the

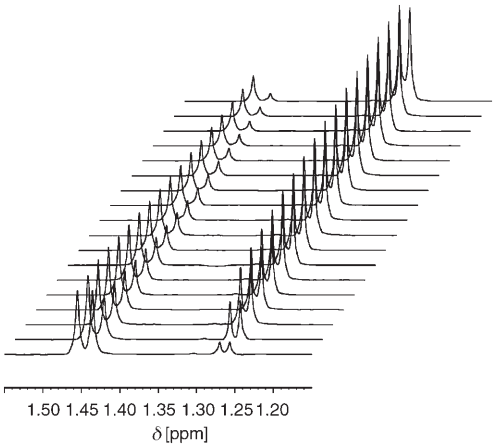


Figure 10. Kinetic resolution in the decarboxylation of the diastereomeric salt formed between the acid **2** and ephedrine, followed by NMR [c(acid) = 0.25 M, 1 equiv EP, solvent: CD_2Cl_2, temperature 30 °C, intervals 2 min].

kinetics of the decarboxylation were followed quantitatively. In addition, the data were confirmed by independent kinetic experiments, in which the samples were quenched with diazomethane and immediately analysed by chiral chromatography. Deracemization of **2** was corroborated by the different concentrations of its methyl esters formed after addition of diazomethane (Figure 11). The kinetic data obtained from derivatization experiments correspond well with those obtained by in situ NMR measurements (not shown). Moreover, the concentrations of the single enantiomers of **4**, and thus the enantioselectivity, could also be followed. Variation of the enantioselectivity with time (conversion) was similar to the patterns shown in Figures 6 and 7: the *ee* decreased sharply at the beginning of the reaction and then increased monotonously at higher levels of conversion.

Origin of enantioselectivity: Kinetic experiments involving in situ NMR analysis and chiral chromatography (after derivatization) indicated that kinetic resolution of the diastereomeric salts formed between the intermediate acid *rac*-**2** and the chiral amino alcohol plays a crucial role in the cascade reaction of **1** to give **4**. The catalytic experiments revealed that at least two equivalents of amino alcohol are required in order to reach the highest enantioselectivity. A plausible explanation may be that one equivalent is required to form a salt with the acid, while the other amino alcohol molecule is responsible for the enantioselective protonation. Note that interactions of amino alcohols, such as cinchona alka-

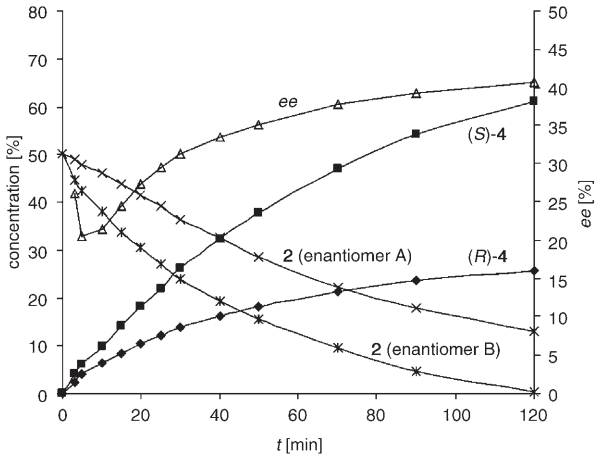


Figure 11. Kinetic resolution of the diastereomeric salt of the acid **2** with QN and the formation of (*R*) and (*S*) enantiomers of the ketone **4** as monitored by chiral GC and HPLC after derivatization with diazomethane. Conditions: **1** (40 mg), QN (1 equiv), CH_2Cl_2 (5 mL), stirring under argon.

loids, with carboxylic acids are rather complex: beside the 1:1 salts, the formation of various cyclic and linear 1:2 base/acid complexes has also been demonstrated by FTIR spectroscopy.[64] Hence, an alternative explanation would be that the high amino alcohol/acid molar ratio favours enantioselectivity due to the preferential formation of the 1:1 amino alcohol/**2** complex. It would be expected that the presence of various amino alcohol/acid complexes possessing rather loose structures[64] should diminish the efficiency of the enantioselection.

In the mechanism of enantioselective decarboxylation proposed by Muzart and Hénin,[25,27] the acid decarboxylates to form an enol or enolate intermediate, which is enantioselectively protonated. This mechanism follows the classical cyclic mechanism of decarboxylation of β-keto esters and malonic acid derivatives.[65,66] The proton of the acid is transferred to the oxygen of the carbonyl group in the β-position through a cyclic six-membered transition state. The transition state decomposition results in the formation of an enol and carbon dioxide. The enol undergoes tautomerization and the ketone is formed. Muzart and Hénin presumed that the enantioselective step is enol tautomerization catalysed by the chiral amino alcohol to form the optically active ketone.[27] The presence of enol intermediate was supported by UV/Vis and NMR spectroscopy.[27] It was suggested that the acid **2** completely transformed into enol **3**, which then reacted slowly to afford ketone **4**. Accumulation of enol **3** was attributed to stabilization by the keto acid **2** and to slow enol–ketone tautomerization.[27] The kinetic analysis of the transformation of **2** to **4**, however, was made under conditions far from those of the catalytic experiments: the substrate concentration was orders of magnitude lower and no chiral amino alcohol was present in the spectroscopic study. Note that the decarboxylation reaction cannot be followed in the presence of an amino alcohol since the UV/Vis spectra of the amino alcohols overlap with those of the keto acid.

Monitoring of the reaction by UV/Vis provided results similar to those reported by Muzart and Hénin.[27] Figure 12 shows the absorption spectra of **2** and **4**. The spectra are very similar to each other and so it is not straightforward to follow the reaction by UV/Vis spectroscopy alone. The reaction of a concentrated keto acid solution (0.04 M **2** in acetonitrile) was monitored by taking samples that were diluted in acetonitrile before analysis. No change in the spectra could be detected during 220 min reaction time (Figure 12). A minor shift of the maximum from 246 to 245 nm was observed only after the concentrated solution had been heated to 70 °C. The new spectrum was similar to that of the ketone **4**, and TLC analysis confirmed the almost complete transformation of **2** into **4**. In agreement with the former report,[27] we could not detect the formation of enol at the high concentration of **2** that is applied in the catalytic reactions.

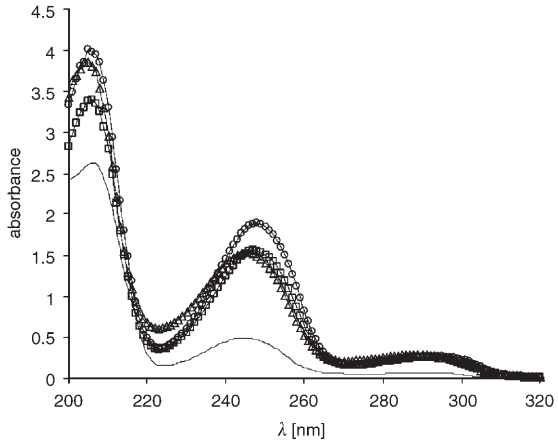


Figure 12. UV/Vis absorption spectra of keto acid **2** and ketone **4**. Conditions: **2** (40 mg), acetonitrile (5 mL), stirring under argon; samples (10 μL) diluted with acetonitrile (3 mL) were measured.

When choosing very low concentrations of **2** ($\leq 5.10^{-4}$ M), we were able to reproduce the interesting oscillation phenomenon reported by Muzart and Hénin[27] well, but the conversion of **2** could not be confirmed by TLC (at 5.10^{-4} M concentration). Moreover, we found a surprising correlation: the (apparent) rate of the conversion of **2** (calculated from the spectra) was diminished by increasing its concentration in the 5.10^{-6} to 5.10^{-4} M range (see Supporting Information). Since it was not possible to analyse samples directly at such low concentrations, we measured the dependence of the rate of decarboxylation of **2** on its concentration in the 5.10^{-3} to 5.10^{-1} M range by GC (after derivatization with diazomethane) and by NMR. We found that in this concentration range the acid reacted more slowly when the concentration was decreased, as expected. Therefore, we believe that decarboxylation of **2** is even slower at the very low concentrations applied in the UV/Vis measurements and that the fas-

cinating phenomenon revealed by UV/Vis spectroscopy[27] is an oscillation reaction.

Our attempt to detect the formation of an enolic species during decarboxylation of **2** by in situ NMR spectroscopy also failed. Experiments carried out with solutions of **2** (0.3 and 0.04 M) in CD_3CN at 25 °C revealed only slow decarboxylation (7% and 3% conversion, respectively, after 3 h) and the corresponding formation of **4**. When the reaction temperature was increased to 50 °C, the decarboxylation proceeded more rapidly, but again, only the formation of **4** could be observed. A possible explanation might be the high reactivity of the enol resulting in rapid tautomerization to the ketone **4**.

We also analysed the decarboxylation of **2** with in situ ATR-IR spectroscopy. The experiments were carried out in the absence (Figure 13) and in the presence of quinine (see Supporting Information). The keto acid **2** displayed three main bands: a broad COOH band at 1720–1760 cm^{-1}, the C=O band at 1691 cm^{-1} and the band of the aromatic ring at 1600 cm^{-1}. The COOH band has two maxima, attributable to the free acid (1743 cm^{-1}) and the hydrogen-bonded acid dimer (1734 cm^{-1}). The signal of the free acid decreased more rapidly than that of the dimer during decarboxylation both with and without QN. The different reaction rates of acid monomer and dimer were even more pronounced at higher acid concentrations (see Supporting Information). The formation of ketone **4** could be monitored through the strengthening of the C=O band at 1684 cm^{-1}. Unfortunately, this band overlaps with the C=O band of **2**, which makes the monitoring of the product formation more difficult. Experiments with 0.3, 1 and 2 equiv of amino alcohol relative to **2** showed similar results. The disappearance of the COOH bands was faster at higher amino alcohol/**2** molar ratios. At the same time, formation of the salt between the acid and the amino alcohol could be observed through the appearance of a broad signal belonging to the carboxylate (asymmetric stretch) in the 1550–1650 cm^{-1} range. Apart from the signals belonging to the acid, carboxylate, ketone and the amino alcohol, only the signal belonging to the CO_2 co-product could be observed. No signals indicative of the enol could be identified during the reaction either in the presence or in the absence of amino alcohol.

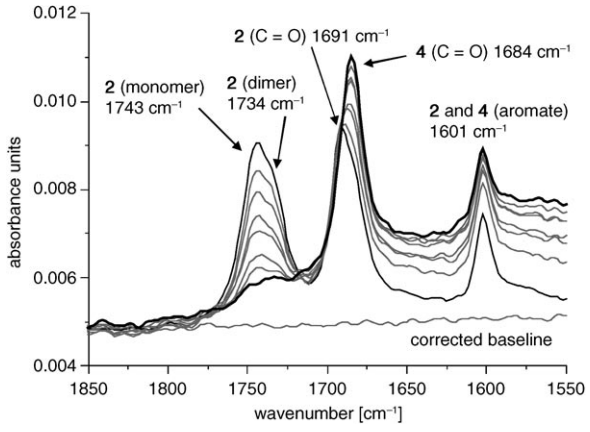


Figure 13. Decarboxylation of keto acid **2** monitored in situ by ATR-IR spectroscopy. Conditions: **2** (100 mg), AcCN ($c = 2.4 \times 10^{-2}$ M, 20 mL), stirred under argon at 50 °C.

As emerges from the results described above, no reliable indication of the formation of an enolic intermediate could be obtained by spectroscopic methods. This failure might be explained in terms of the immediate transformation of the enolic species into the thermodynamically favoured ketone. We prefer another interpretation, though: the direct protonation of the carbon atom at C(2) by the chiral amino alcohol, simultaneously with the breaking of the C–C bond between C(2) and the carboxylate. These steps might proceed as a concerted mechanism, in which the protonation would always take place from the free side of the molecule: that is, from the opposite side of the carboxylate. A similar mechanism has been suggested by Drees et al. for the enantioselective decarboxylation of a Naproxen intermediate.[67]

Conclusion

Our mechanistic study indicates that deprotection (debenzylation) of **1** occurs on the Pd surface, but that the decarboxylation step is catalysed homogeneously in the liquid phase by the chiral amino alcohol ("chiral inductor"). In addition, kinetic resolution of the diastereomeric salt of the racemic acid and the chiral amino alcohol plays a key role in the enantioselectivity. The kinetic resolution proceeds homogeneously in solution and not at the metal surface. Thus, in contrast with various enantioselective hydrogenation reactions on Pd in the presence of a cinchona alkaloid, decarboxylation of **2** is not a metal-catalysed route but an organocatalytic process.

Experimental Section

Chemicals: Ephedrine (>95%), quinine (>99%), quinidine (>99%), cinchonine (>98%) and cinchonidine (>98%), Pd/C catalyst (5 wt%, Fluka), acetonitrile (>99.5%), methylene chloride (>99.5%), hexane (HPLC grade) and propan-2-ol (HPLC grade) were all supplied by Fluka. Hydrogen (99.999%) and argon (99.999%) were purchased from Pangas.

Synthesis of starting materials: Compounds **1** and **2** were prepared by slightly modified methods described elsewhere.[27,35] 2-Methyl-1-tetralone-2-carboxylic acid benzyl ester (**1**) was prepared by acylation of 1-tetralone with diethyl carbonate and sodium hydride followed by methylation with methyl iodide under PTC conditions and transesterification with benzyl alcohol catalysed by titanium isopropoxide. Later, we used a procedure with the last two steps exchanged: transesterification of 1-tetralone-2-carboxylic acid ethyl ester was carried out first to provide 1-tetralone-2-carboxylic acid benzyl ester, which was subsequently methylated. The latter procedure was easier to carry out and gave higher yields. 2-Methyl-1-tetralone-2-carboxylic acid (**2**) was prepared by saponification of 2-methyl-1-tetralone-2-carboxylic acid methyl ester with KOH in methanol, followed by acidification and crystallization of the pure carboxylic acid **2**. The acid is unstable at room temperature and undergoes spontaneous decarboxylation to the ketone **4** and CO_2. To avoid decomposition, the acid was stored at −20 °C. Diazomethane solution in diethyl

ether was prepared from Diazald 214 by the standard procedure.[68] Detailed description of the preparation of all starting materials together with their characterization is provided as Supporting Information.

Typical decarboxylation procedure

a) Starting from 1: The experiments were carried out in a 50 mL glass reactor with heating and magnetic stirring. The catalyst (5 wt% Pd/C) and the chiral amino alcohol (0.3 equiv relative to substrate) were introduced into the reactor together with the solvent (acetonitrile, 5 mL), after which the reactor was flushed with argon and hydrogen and the mixture was stirred at the reaction temperature under a flow of hydrogen for 10 min. The reaction was started by addition of **1** (100 mg, 0.34 mmol), dissolved in acetonitrile (5 mL), by syringe under hydrogen. Samples withdrawn during the reaction were filtered and analysed by GC, chiral HPLC and GC-MS.

b) Starting from 2: The chiral amino alcohol (1 equiv relative to the substrate) and the solvent (acetonitrile, 4 mL) were stirred magnetically in a 25 mL round flask under argon at room temperature. The reaction was started by addition of the acid **2** (40 mg, 0.2 mmol) dissolved in acetonitrile (1 mL) by syringe under argon. Excesses of ethereal diazomethane solution were added to the samples withdrawn during the reaction, in order to quench the reaction before chromatography. Unreacted acid **2** was thus immediately and completely transformed into its methyl ester. This procedure allowed us not only to monitor the reaction rate of decarboxylation, but also to measure the *ee* of the methyl ester of the acid **2**.

Analysis: The reaction mixtures were analysed with the aid of a Trace GC (Thermo Finnigan) gas chromatograph with an Agilent HP-5 capillary column (30 m × 0.32 mm × 0.25 μm). Chromatograms were acquired under the following conditions: injector 260 °C, detector 260 °C, 50 kPa He, flow 1.5 mL min^{-1}, temperature program: 80 °C for 2 min, then 20 °C min^{-1} to 300 °C. The *ee* of **4** was determined by HPLC with a Merck LaChrom system. The analysis was carried out on a Chiracel OD (240 mm × 4.6 mm i.d., 10 μm particle size) chiral column at 25 °C with a liquid flow rate of 0.9 mL min^{-1} and an *n*-hexane/propan-2-ol 9:1 mixture as eluent. Retention times: 7.2 min (*R*)-**4**, 7.8 min (*S*)-**4**, 13.3 and 14.5 min (*R*) and (*S*) enantiomers of **1** (not assigned). The samples withdrawn from the reaction mixtures were also analysed with an Agilent GC-MS (HP 6890 MSD) with an HP-5 MS column (30 m × 0.25 mm × 0.25 μm). Elementary analysis (Leco CHN-900 and Leco RO-478 automatic analysers) and ^{1}H and ^{13}C NMR spectroscopy (Bruker AG DPX 300 and AVANCE 500) were carried out to characterize all prepared compounds. The decarboxylation of **2** was followed in situ by NMR, UV and ATR-IR spectroscopy with an AVANCE 500 instrument (Bruker AG), a Cary 400 Scan UV/Visible spectrophotometer and an IFS66 spectrometer (Bruker Optics) fitted with a commercial mirror unit (Specac) and a liquid nitrogen-cooled HgCdTe detector, respectively.

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