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Structural effects in the Pd-induced enantioselective deprotection–decarboxylation of β-ketoesters

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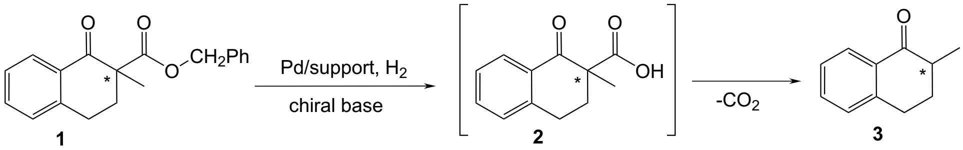
Abstract—Structural effects in the chiral base and the influence of some key reaction parameters (catalyst type and solvent) in the Pd-induced enantioselective decarboxylation (cascade reaction) of three different α,α-disubstituted benzyl β-ketoesters were explored. The reaction intermediate after debenzylation (β-keto-carboxylic acid) was synthesized and its decarboxylation studied independently. The highest ee (up to 60%) in the cascade reaction was achieved with those substrates that contained an aromatic ring system and with chiral amino alcohols that possessed an extended aromatic ring (quinine and quinidine). Polar solvents with weak H-bond donor and acceptor properties favor enantioselection.

1. Introduction

The application of one-pot domino, or cascade, reactions is a highly attractive route to the synthesis of complex chiral molecules.[1] An interesting example, the deprotection, enantioselective decarboxylation reaction series leading to optically active carbonyl compounds, has been intensively investigated by Henin, Muzart, et al.[2–7] The key intermediate, a β-ketoacid, can be produced in situ by a Pd-catalyzed deprotection of a benzyl (or allyl) β-ketoester (Scheme 1) and the enantioselective decarboxylation is assisted by a chiral amino alcohol or amine. The amount of chiral base varies between stoichiometric and catalytic (0.15–0.3 equiv);[4–6,8] the latter ratio requires the proper choice of catalyst and reaction conditions. Various chiral amino alcohols and amines are suitable as a part of the catalyst system,[2,7,9] but the ee rarely exceeds 80%. In the case of chiral amino alcohols, the absolute configuration of the ketone depends upon the configuration of the carbon carrying the amino group, not the OH group, of the modifier.[2] It has been found that the type of the supported Pd catalyst significantly influences the reaction rate and the enantioselectivity, which might indicate the key role of Pd in the cascade reaction.[6,7,9,10]

In a mechanistic study, Detalle et al.[2–7] concluded that the cascade reactions afforded the chiral ketone via Pd-catalyzed decarboxylation and enol isomerization. In the reinvestigation of some of these cascade reactions, we found strong indications that the role of Pd is probably



Scheme 1. Domino reaction of **1** to **3** catalyzed by supported Pd and a chiral amine or amino alcohol (see Figs. 1 and 2).

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limited to the first step, the debenzylation of the benzyl (or allyl) β-ketoester. Herein, we report the first part of our study, focusing on the key structural effects that control the stereochemical outcome of the reaction: the structure of the substrate and the chiral base, and also the properties of the solvent. To support these conclusions, we have included in this study a broad range of chiral amines and amino alcohols, which have already been applied in these types of cascade reactions, although mainly not in the transformation of the substrates used in this work.

2. Results and discussion

2.1. The role of the chiral base

Various chiral amines and amino alcohols were tested in the cascade reaction of **1** to find a relationship between their molecular structure and the enantioselectivity (Figs. 1 and 2). It has been shown in the cascade reactions of benzyl β-ketoesters,[8] that amino alcohols afford far better enantioselectivities than amines; this conclusion is fully

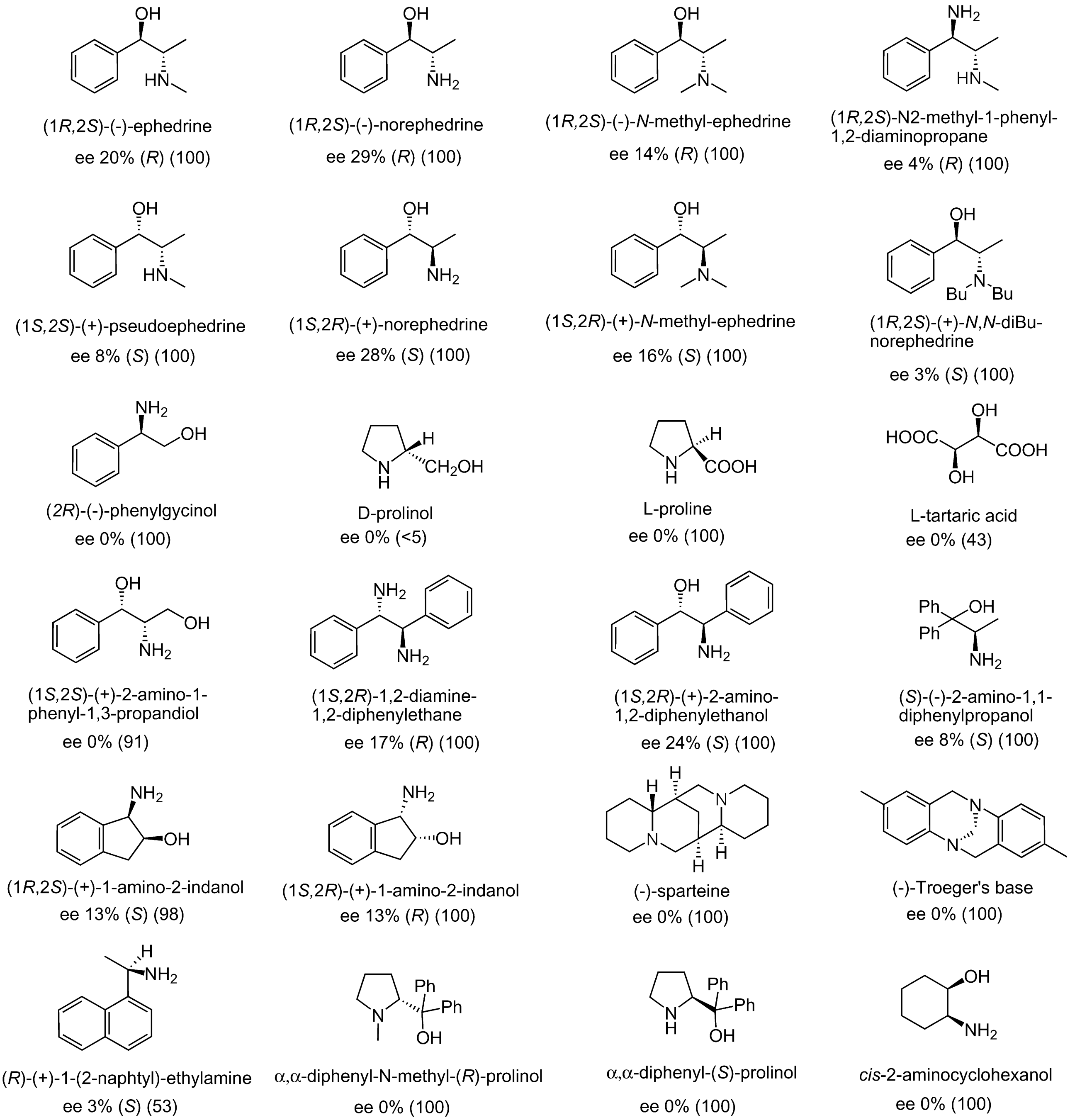
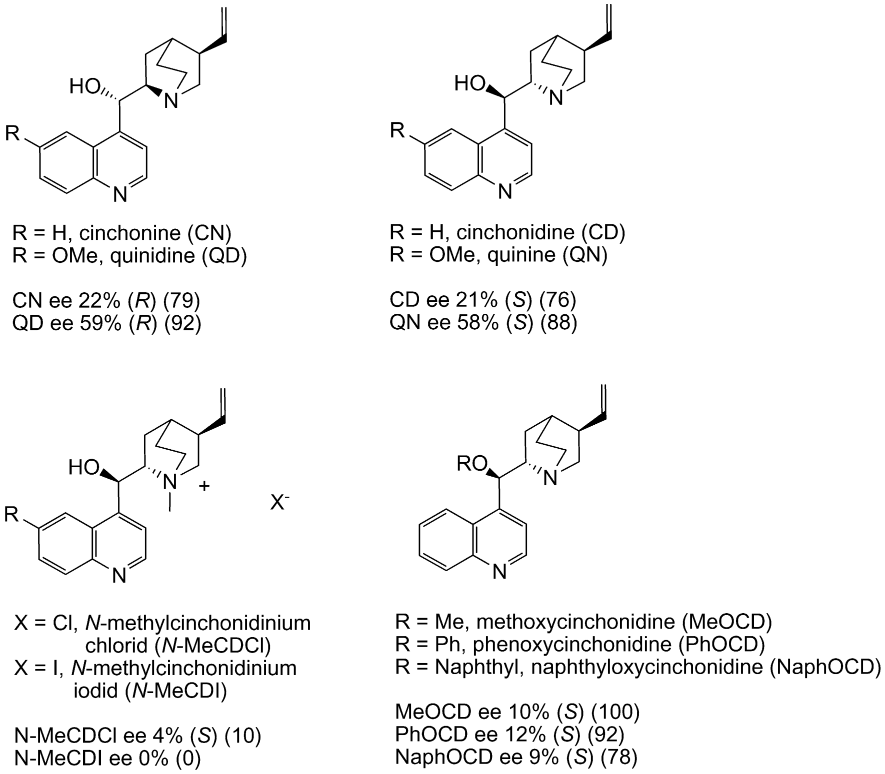


Figure 1. Chiral amines and amino alcohols tested in the transformation of **1** (Scheme 1). The number in brackets after the ee indicates the conversion. Reaction conditions: 20 mg **1**, 0.025 equiv Pd, 0.3 equiv alkaloid, 2 mL MeCN, room temperature, 1 bar, H_2, 2 h.



R = H, cinchonine (CN)
R = OMe, quinidine (QD)

CN ee 22% (*R*) (79)
QD ee 59% (*R*) (92)

R = H, cinchonidine (CD)
R = OMe, quinine (QN)

CD ee 21% (*S*) (76)
QN ee 58% (*S*) (88)

X = Cl, *N*-methylcinchonidinium chlorid (*N*-MeCDCl)
X = I, *N*-methylcinchonidinium iodid (*N*-MeCDI)

N-MeCDCl ee 4% (*S*) (10)
N-MeCDI ee 0% (0)

R = Me, methoxycinchonidine (MeOCD)
R = Ph, phenoxycinchonidine (PhOCD)
R = Naphthyl, naphthyloxycinchonidine (NaphOCD)

MeOCD ee 10% (*S*) (100)
PhOCD ee 12% (*S*) (92)
NaphOCD ee 9% (*S*) (78)

Figure 2. Derivatives of cinchona alkaloids and their performance in the debenzylation–decarboxylation of **1** (Scheme 1). The number in brackets after the ee indicates the conversion. Reaction conditions: 20 mg **1**, 0.025 equiv Pd, 0.3 equiv alkaloid, 2 mL MeCN, room temperature, 1 bar, H_2, 2 h.

confirmed by our results. The highest ee was obtained with amino alcohols with a defined configuration at both stereogenic centers. A comparison of the primary, secondary, and tertiary amino groups showed that the enantioselectivity decreased in this order (see norephedrine, ephedrine, and *N*-methyl-ephedrine in the first row of Fig. 1). Furthermore, the larger the nitrogen substituent, the lower was the enantioselectivity, cf. *N*-methyl-ephedrine with *N*,*N*-dibutyl-norephedrine. This relationship was, however, only valid for ephedrine derivatives; cinchona alkaloids containing an isoquinoline ring and a rigid tertiary amino group provided higher enantioselectivity (Fig. 2). Substitution of the aromatic ring with a methoxy group (cinchonine→quinidine, cinchonidine→quinine) almost tripled the ee (Fig. 2). Replacement of the hydroxyl group of cinchonidine with methoxy, phenoxy, and naphthoxy substituents diminished the enantioselectivity, independent of the steric bulkiness of the ether function. N-Alkylation of cinchonidine led to (almost) complete loss of ee.

From all the chiral bases tested, the highest enantioselectivities were achieved with the rigid structures of cinchona alkaloids (almost 60% using quinine and quinidine); ephedrine derivatives were less efficient (14–30%). Another important difference between ephedra and cinchona derivatives is the opposite effect of the amino alcohol configuration on the stereochemistry of the product: while the (1*R*,2*S*)-configuration of ephedrine gives the (*R*)-ketone, the same configuration of cinchona alkaloid (e.g., quinine and cinchonidine) gives the (*S*)-product. This may be a valuable observation for future mechanistic studies.

Screening of various amino alcohols indicates that the rigidity of the C–C bond between C-atoms bearing the amino and hydroxyl groups and the presence of an extended aromatic system seem to play an important role in the enantioselection.

2.2. The effect of Pd catalyst

A comparison of various commercial catalysts with different Pd loadings and supports in the cascade reaction of **1** to **3** is presented in Figure 3. The most active Pd catalysts were those supported on C, TiO_2, and Al_2O_3. Apparently, higher enantioselectivities were obtained on the less active Pd catalysts supported on $CaCO_3$, SiO_2, or $BaSO_4$, which did not provide full conversion within 2 h.

We can speculate that a fast debenzylation of the substrate, relative to the rate of decarboxylation, leads to high actual concentration of the intermediate ketoacid **2**. The resulting low actual chiral amino alcohol/**2** ratio in the reaction mixture is detrimental to the enantioselection, although it can be compensated for with a higher (not catalytic) initial amino alcohol/**1** ratio. It should be noted that the influence of the type and source of supported Pd, observed in former studies[6,7,9,10] may be used as indirect evidence for the critical role of Pd as the catalyst in the whole cascade reaction series. In contrast, our opinion is that Pd controls, via the deprotection step, only the actual concentration of the ketoacid and thus the chiral base/ketoacid ratio; the latter has a strong influence on the enantioselectivity.

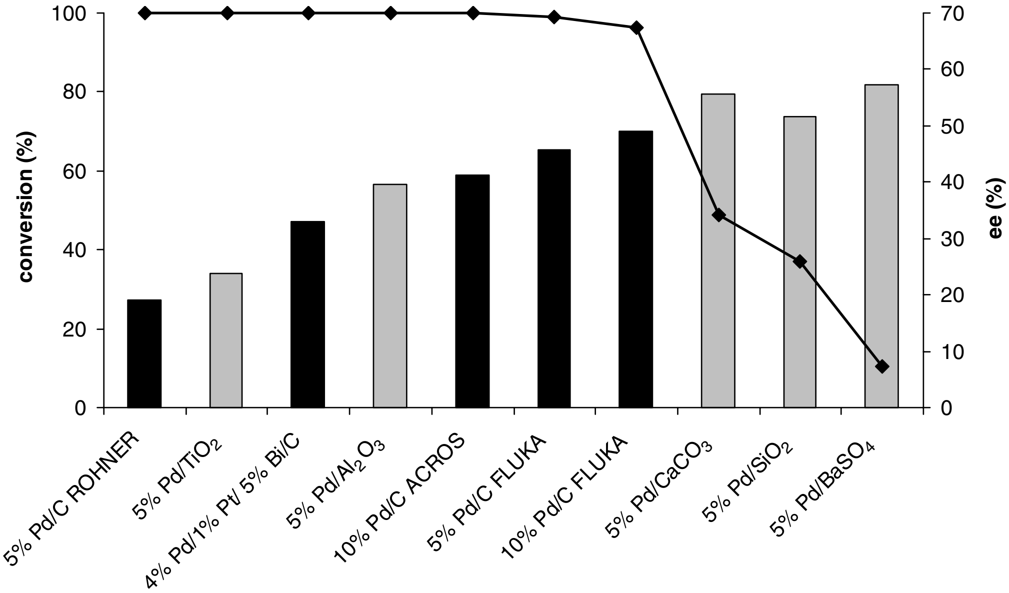


Figure 3. Effect of catalyst composition on conversion (◆) and ee (columns) of debenzylation–decarboxylation of **1**. Reaction conditions: 20 mg **1**, 0.025 equiv Pd, 0.3 equiv quinine, 2 mL MeCN, room temperature, 1 bar, H_2, 2 h. Ee achieved with C-supported Pd catalysts is represented by black columns.

2.3. Solvent effect

Preliminary experiments on the cascade reaction of **1** to **3** revealed a dramatic influence of the solvent, including its purity, on the enantioselectivity. In the case of acetonitrile, the ee strongly depended on the water content. The addition of one drop of water to our standard reaction mixture prepared with dry acetonitrile resulted in a drop of ee from 58% to 27% ee. It should be noted that commercial carbon-supported Pd usually contains 5–10 (sometimes up to 50) mass% water, which can contribute to the large differences observed among different Pd/C catalysts (Fig. 3).

The enantioselectivities, ordered according to decreasing reaction rates, are shown in Figure 4 for a broad range of solvents. The highest conversion and lowest enantioselectivity were achieved in protic polar solvents. Apparently, these solvents are suitable for the debenzylation

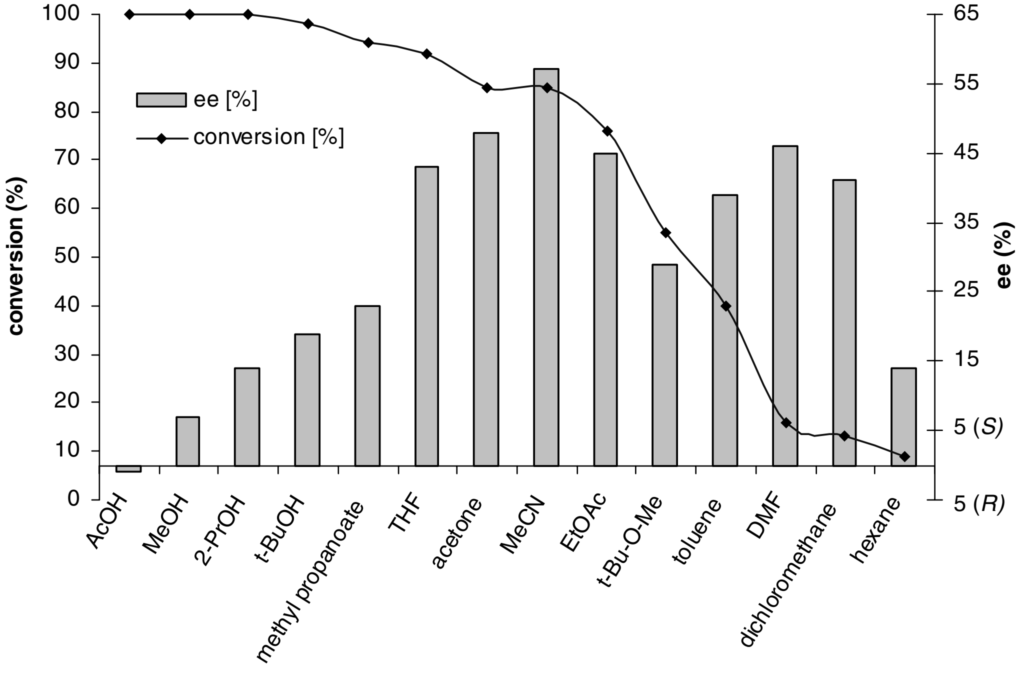


Figure 4. Solvent effect on the conversion and enantioselectivity in the cascade reaction of **1** to **3**. Reaction conditions: 20 mg **1**, 0.025 equiv Pd (5 wt % Pd/C, Fluka), 0.3 equiv quinine, 2 mL MeCN, room temperature, 1 bar, H_2, 2 h.

reaction and rapidly provide the key intermediate **2**, although they are less appropriate for the enantioselective decarboxylation step. In some cases, even the major enantiomer was inverted. An example is the transformation of **1** with Pd/C and cinchonidine: the ketone (*S*)-**3** was formed in acetonitrile, while (*R*)-**3** was the major product in *t*-butanol, both with the same ee of 12%. Inversion was also observed in these experiments when cinchonidine was replaced by cinchonine.

The solvent effect is less clear on the 'right side' of Figure 4, because the conversion varies in this region and the solvent effect may be substantially different in the debenzylation and decarboxylation steps.

2.4. Solvent effect in the decarboxylation of 2

To find a more reliable correlation between the solvent properties and the enantioselection, the reaction intermediate **2** was synthesized and the solvent effect studied independently of the deprotection step of the cascade reaction. It should be noted that **2** is unstable at room temperature and has to be stored at −20 °C. Its decomposition is, however, orders of magnitude slower in the absence of a chiral base or solvent (diluent) than under reaction conditions. For example, under reaction conditions, in acetonitrile, only 5% of **2** decomposed in 2.5 h while the reaction was complete in about 1 h in the presence of 1 equiv quinine (see Fig. 5).

Preliminary experiments in acetonitrile revealed that a much higher concentration of amino alcohol ($\geqslant$1 equiv relative to **2**) is required to obtain reasonable enantioselectivity. For example, the enantioselective decarboxylation of **2** with 1 equiv of quinine in acetonitrile gave 35% ee of (*R*)-**4** at almost complete conversion (98%) and high yield (95%). When the reaction was repeated with only 0.3 or 0.1 equiv of quinine, the ee dropped to 19.5% and 9.5%, respectively. The probable explanation is that in the cascade reaction, intermediate **2** is produced slowly by deprotection of **1** while the actual molar ratio of the chiral base to **2** is much higher than the initial chiral base/**1** ratio.

The effect of solvent on the conversion and enantioselectivity in the decarboxylation of **2** is shown in Table 1. To compare the reaction rates in different solvents, in one series of experiments the reaction was stopped after 15 min. Conversions higher than 70% were reached with the majority of the solvents. The enantioselectivities measured after 15 min (e_x) varied remarkably, and in toluene even the opposite enantiomer of **3** was obtained. At complete conversion there was a reasonably good correlation between the enantioselectivity (ee_{100}) and solvent properties characterized by the empirical solvent parameter (E_{T}^{N}) for polarity, and the Kamlet–Taft solvent parameters α and β for the H-bond donor and acceptor strength, respectively. The highest enantioselectivity was obtained in those polar solvents, which are poor H-bond donors and acceptors. Chloroform and dichloromethane were the best solvents: their polarity is moderate but they are poor H-bond donors and acceptors. Unfortunately, chlorinated solvents are not appropriate for the cascade reaction, since their slow dehalogenation with the Pd/H system leads to HCl formation and catalyst deactivation. Acetonitrile and acetone were also good solvents for the decarboxylation of **2**: they are sufficiently polar but are weak H-bond donors and acceptors. The ee was significantly lower in protic polar solvents (*t*-butanol) and in weak polar solvents (toluene). A feasible explanation for the solvent effect is that a polar solvent could stabilize the substrate-chiral base interaction but not distort it with additional H-bonding interactions.

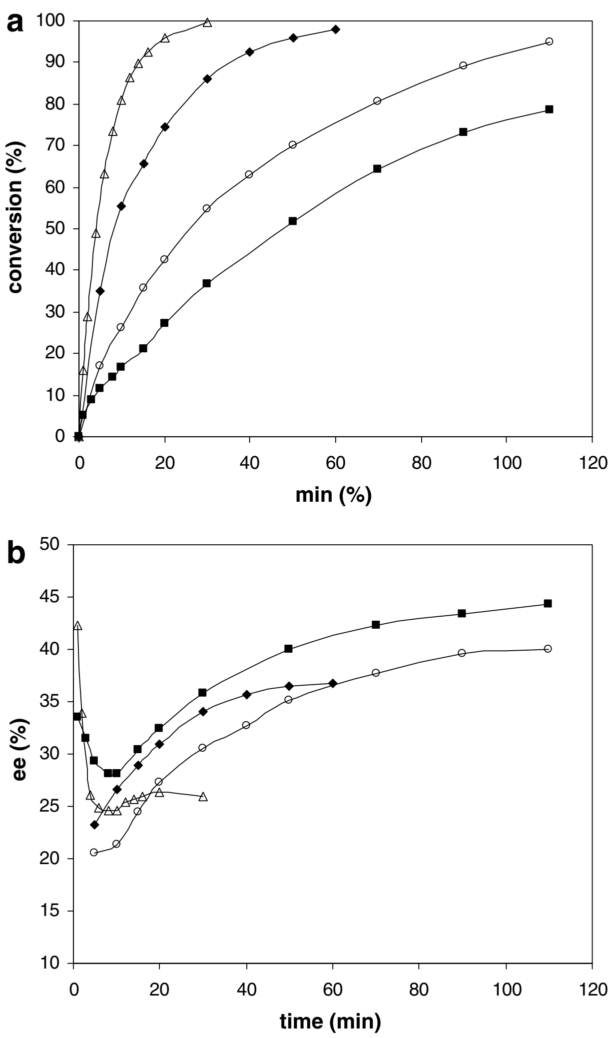


Figure 5. The effect of solvent on the rate (a) and enantioselectivity (b) in the decarboxylation of **2**; ◆—acetonitrile, ■—chloroform, △—ethyl acetate, ○—dichloromethane. Reaction conditions: 40 mg **2**, 63.5 mg (1.0 equiv) quinine, 5 mL solvent.

As it can be seen in Table 1, the enantioselectivity varies with conversion and the solvent has a big influence on this correlation. A more detailed analysis is shown in Figure 5 for four different solvents. The samples were withdrawn from the reaction mixture and quenched with diazomethane to stop the conversion of **2** while the amount of **2** was determined as its methyl ester. The rate of decarboxylation decreased in the order: ethyl acetate > acetonitrile > dichloromethane > chloroform. The enantioselectivity changed significantly with time; it reached a minimum at

Table 1. Influence of solvent properties on the conversion of **2** and the enantioselectivity to (*S*)-**3**

Solvent	Polarity (E_T^N)	α (Taft)	β (Taft)	*X* (%)	ee_x (%)	ee_{100} (%)
MeCN	0.460	0.19	0.40	56	30	34
t-BuOH	0.389	0.42	0.93	14	24	16
Acetone	0.355	0.08	0.48	93	35	36
CH_2Cl_2	0.309	0.13	0.10	34	14	38
$CHCl_3$	0.259	0.20	0.10	17	24	44
EtOAc	0.228	0.00	0.45	93	23	23
THF	0.207	0.00	0.55	100	18	20
Dioxane	0.164	0.00	0.37	82	14	12
Et_2O	0.117	0.00	0.47	90	12	16
Toluene	0.099	0.00	0.11	71	10[a]	4

X—conversion after 15 min, ee_x—ee after 15 min, ee_{100}—ee at 100% conversion. Reaction conditions: 5 mg **2**, 8 mg (1.0 equiv) quinine, 2 mL solvent.

[a] Product with (*R*)-configuration.

the beginning of the reaction, and then increased until complete conversion.

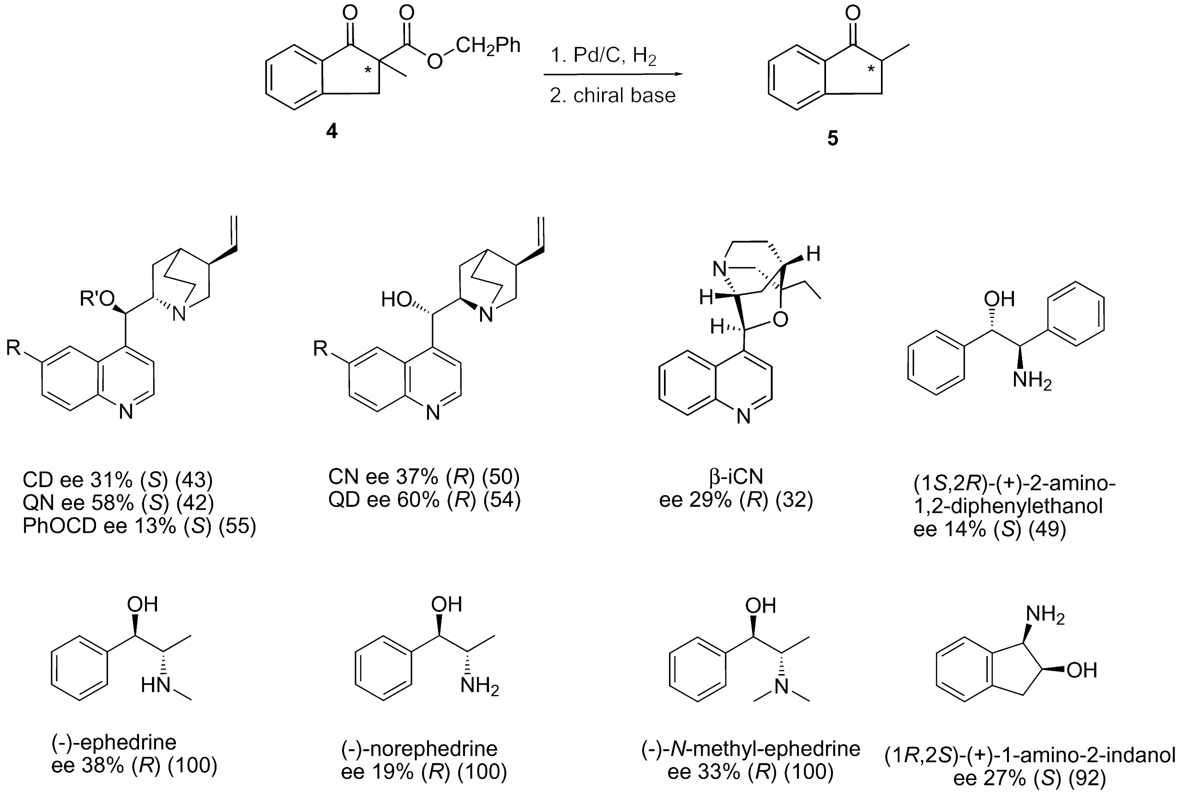
2.5. Effect of substrate structure

The debenzylation–decarboxylation of **4** was studied using the most promising chiral amino alcohols (Fig. 6). The same reaction conditions were applied as in the transformation of **1** (Figs. 1 and 2) to allow comparison of the results. When using cinchona alkaloids as chiral bases, the reactivity of **4** was lower than that of **1** but the enantioselectivities were similar or slightly better. The best chiral bases were again quinine (58% ee) and quinidine (60% ee). The transformation of cinchonine to the rigid β-*iso*-cinchonine resulted in some loss of ee. The efficiency of ephedrine derivatives changed significantly: the highest ee (38%) was obtained with ephedrine, not with norephedrine. In general, the results in Figures 1, 2 and 6 show that although the effect of the chiral base is substrate dependent, for the similar substrates **1** and **4** the differences are not big.

Finally, another α-disubstituted β-ketoester (substrate **6** in Fig. 7) that possesses no aromatic functionality was chosen. The structural differences between **1** and **6** are reflected by the results in Figures 1, 2, and 7: in most cases, the reaction rates are somewhat higher while the enantioselectivities are considerably lower in the cascade reaction **6** to **7**. An exception was the reaction in the presence of β-*iso*-cinchonine, which was the most efficient chiral base in this series. We assume that the generally poor enantioselectivities are mainly due to the missing aromatic function in **6**.

3. Conclusions

The enantioselective one-pot debenzylation–decarboxylation of α-disubstituted β-ketoesters **1**, **4**, and **6** was (re)investigated on supported Pd catalysts, in the presence of a broad range of chiral amines and amino alcohols. The best enantioselectivities up to 60% were achieved with quinine and quinidine. Efficient enantioselection required at least equimolar amount of the chiral base related to the ketoacid intermediate and a polar solvent that does



CD ee 31% (*S*) (43)
QN ee 58% (*S*) (42)
PhOCD ee 13% (*S*) (55)

CN ee 37% (*R*) (50)
QD ee 60% (*R*) (54)

β-iCN
ee 29% (*R*) (32)

(1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol
ee 14% (*S*) (49)

(-)-ephedrine
ee 38% (*R*) (100)

(-)-norephedrine
ee 19% (*R*) (100)

(-)-*N*-methyl-ephedrine
ee 33% (*R*) (100)

(1*R*,2*S*)-(+)-1-amino-2-indanol
ee 27% (*S*) (92)

Figure 6. Various chiral amino alcohols tested in the enantioselective debenzylation–decarboxylation of **4**. The number in brackets after the ee indicates the conversion. Reaction conditions: 20 mg **4**, 0.025 equiv Pd (5 wt % Pd/C, Fluka), 0.3 equiv quinine, 2 mL MeCN, 1 bar H_2, room temperature, 2 h.

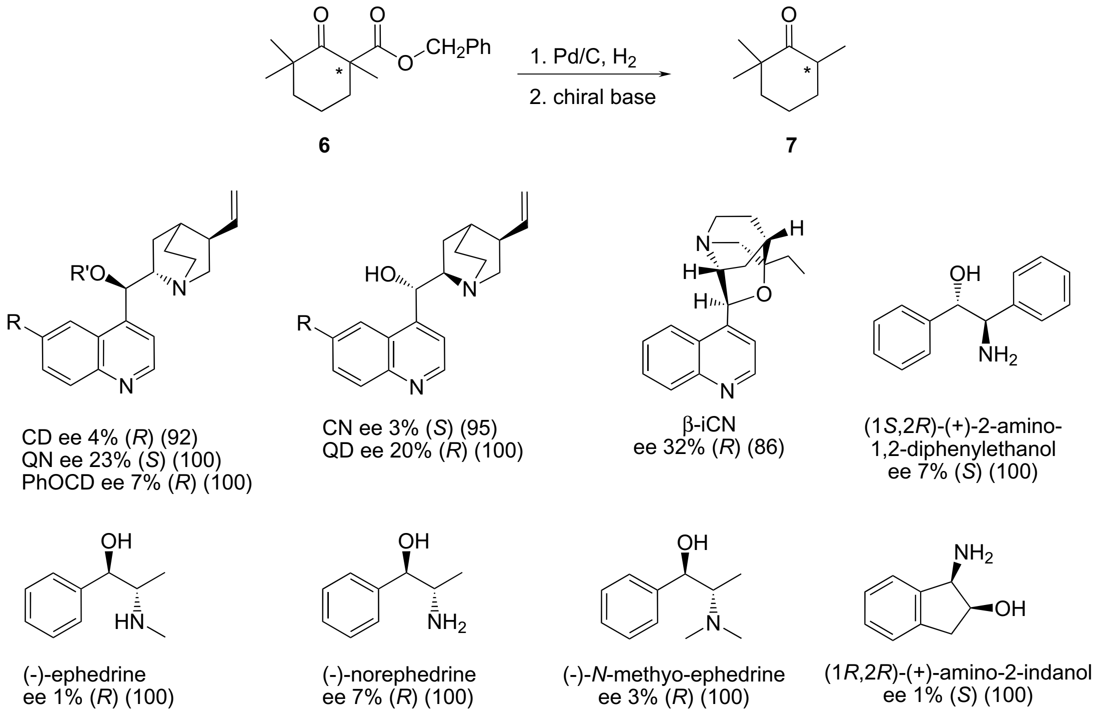


Figure 7. Various chiral amino alcohols tested in enantioselective debenzylation–decarboxylation of **6**. The number in brackets after the ee indicates the conversion. Reaction conditions: 20 mg **6**, 0.025 equiv Pd (5 wt % Pd/C, Fluka), 0.3 equiv quinine, 2 mL MeCN, room temperature, 1 bar H_2, 2 h.

not promote H-bonding interactions. The enantioselectivity was considerably higher when an aromatic ring was present in the substrates **1** and **4** and an extended aromatic ring in the chiral base (cinchona alkaloids). The observation may indicate that the cascade reaction is triggered by debenzylation on the Pd surface, but the subsequent decarboxylation occurs in solution by the interaction of the chiral base (being present in at least stoichiometric amounts) and the ketoacid. The structural effects in the substrate and chiral base, the high base/ketoacid ratio, and the solvent effect suggest that the chiral base–ketoacid interactions involve a π-bonding interaction and also H-bonds. It is also known that quinine and quinidine adsorb more weakly on Pd than cinchonidine and cinchonine.[11] Hence, doubling the enantioselectivity when replacing cinchonidine or cinchonine by the aryl-substituted alkaloids quinine or quinidine (Figs. 2 and 6) supports the assumption that decarboxylation does not occur on the Pd surface (involving Pd as the active species and the chiral base as a chiral surface 'modifier'), but rather the origin of enantioselection is the decarboxylation in solution catalyzed by the chiral base being present in at least equimolar amounts.[8,12] More evidence in this direction, based on catalytic and spectroscopic studies, will be reported in the second part of our work.[13]

4. Experimental

4.1. General

All samples were analyzed by gas chromatography using a Trace GC (Thermo Finnigan) gas chromatograph equipped with Agilent capillary column HP-5 (30 m × 0.32 mm × 0.25 μm). The intermediates and products of the reactions were analyzed by an Agilent GC–MS (HP 6890 MSD) equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm). Separations were carried out by column chromatography (Fluka Silica Gel 60 (0.04–0.063 mm); solvent: 8:2 hexane/ethyl acetate) and the products were analyzed by TLC (Merck TLC plates pre-coated with Silica Gel 60 F_{254}; visualization by treatment with Mostain solution). After separation and isolation of the pure compounds, elementary analysis (automatic analyzers Leco CHN-900 and Leco RO-478) and ^{1}H and ^{13}C NMR spectroscopy (DPX 300 and AVANCE 500 from Bruker AG) were used to characterize all compounds prepared. The enantiomeric excess (ee) was determined by GC and HPLC using a Trace GC (Thermo Finnigan) and a Merck LaChrom system, respectively. The analysis was carried out on a GC Chrompack capillary column CP-Chirasil-Dex CB (25 m × 0.25 mm × 0.25 μm) and HPLC chiral column Chiracel OD (240 mm × 4.6 mm i.d., 10 μm particle size).

4.2. Chemicals

The majority of chiral amines and amino alcohols tested are commercially available. The methoxy-, phenoxy-, and naphthoxy-cinchonidine,[14] as well as N-methyl cinchonidinium chloride and iodide,[15] and β-isocinchonine[16,17] were prepared as described elsewhere. All other chiral amines were commercial products and used as received. Palladium catalysts were supplied by various catalyst producers: 5 wt % Pd/C (Fluka: F75992, Rohner: E101 O/W); 10 wt % Pd/C (Fluka: F75990, Acros: A020058801);

5 wt % Pd/SiO_2 (Strem: 46-2090); 5 wt % Pd/TiO_2 (Engelhard: 44057); 5 wt % Pd/Al_2O_3 (Engelhard: 40692); 5 wt % Pd/$CaCO_3$ (Engelhard: 737); 5 wt % Pd/$BaSO_4$ (Engelhard: 2190); 4 wt % Pd/1 wt % Pt/5 wt % Bi/C (Degussa: 1319). The solvents used for the synthesis and catalysis were dried by standard procedures. The preparation of starting materials was carried out under argon. Hydrogen (99.999%) and argon (99.999%) were purchased from Pangas.

4.3. Synthesis of the starting materials

Compounds **1**, **2**, **4**, and **6** were prepared by slightly modified methods described elsewhere.[3,8] Diazomethane solution in diethyl ether, used for quenching the decarboxylation of **2**, was prepared from Diazald 214 using the standard procedure.[18]

4.3.1. 1-Tetralone-2-carboxylic acid ethyl ester 8. 1-Tetralone (21.8 g, 149 mmol) was added dropwise to a stirred suspension of NaH (60% dispersion in oil, 1.3 equiv, 8.0 g, 0.2 mol) in dry diethyl carbonate (5.0 equiv, 97.5 g, 100 mL, 825 mmol) under Ar. The reaction mixture was heated at reflux and a white-violet solid was formed. After 1 h at reflux, the mixture was cooled down to 5 °C and 200 mL of 2 M HCl was added dropwise while stirring. The solid was dissolved and the phases separated. The aqueous phase was extracted (2×) with toluene. The combined extracts were dried over $MgSO_4$ and evaporated in vacuum to give a brown oil (30.2 g). The crude product was purified by flash chromatography (petrol ether/ethyl acetate, 9:1) to give 24.0 g (73% yield) of 2-carboethoxy-1-tetralone. The keto/enol ratio was approximately 1:2. The spectroscopic data were in agreement with those published elsewhere.[1] ^{1}H NMR (500 MHz, $CDCl_3$): 1.28 (t, $J = 7.1$ Hz, Me, 3H, ketone), 1.32 (t, $J = 7.1$ Hz, Me, 3H, enol), 2.30–2.35 (m, H–C(3), 1H, ketone), 2.40–2.50 (m, H–C(3), 1H, ketone), 2.53–2.57 (m, H–C(3), 2H, enol), 2.77–2.80 (m, H–C(4), 2H, enol), 2.93–3.06 (m, H–C(4), 2H, ketone), 3.57 (dd, $J = 4.7$, 10.5 Hz, H–C(2), 1H, ketone), 4.12–4.31 (m, OCH_2, 2H, ketone), 4.26 (q, $J = 7.1$ Hz, OCH_2, 2H, enol), 7.14 (dd, $J = 0.8$, 7.2 Hz, H–C(5), 1H, enol), 7.21 (d, $J = 7.7$ Hz, H–C(5), 1H, ketone), 7.23–7.31 (m, H–C(6,7), 3H, ketone and enol), 7.45 (td, $J = 1.5$, 7.9, H–C(7), 1H, ketone), 7.78 (dd, $J = 1.4$, 7.5 Hz, H–C(8), 1H, enol), 8.03 (dd, $J = 1.1$, 7.9 Hz, H–C(8), 1H, ketone), 12.50 (s, OH, 1H, enol). ^{13}C NMR (125 MHz, $CDCl_3$): 14.2 (q, Me, ketone), 14.3 (q, Me, enol), 20.6 (t, C(3), enol), 26.4 (t, C(3), ketone), 27.6 (t, C(4), keto), 27.8 (t, C(4), enol), 54.6 (d, C(2), keto), 60.5 (t, OCH_2, enol), 61.2 (t, OCH_2, keto), 97.0 (s, C(2), enol), 124.3 (d, C(8), enol), 126.5 (d, C(6), enol), 126.9 (d, C(6), ketone), 127.4 (d, C(5), enol), 127.7 (d, C(8), ketone), 128.8 (d, C(5), ketone), 130.1 (s, C(4a), enol), 130.5 (d, C(7), enol), 131.8 (s, C(4a), ketone), 133.8 (d, C(7), ketone), 139.4 (s, C(8a), enol), 143.7 (s, C(8a), ketone), 165.0 (s, C(1), enol), 170.2 (s, OC=O, ketone), 172.7 (s, OC=O, enol), 193.2 (s, C(1), ketone).

4.3.2. 2-Methyl-1-tetralone-2-carboxylic acid ethyl ester 9. Ethyl ester **8** (20 g, 92 mmol) was dissolved in toluene (500 mL) and an aqueous 50% NaOH solution (250 mL) was added dropwise under vigorous mechanical stirring. After stirring for 1 h, three portions of tetrabutylammonium bromide (1 g each, ca. 0.1 equiv) were added at intervals of 30 min. Then, methyl iodide (75 mL, 171 g, 13 equiv) was added dropwise within 1 h and the mixture was stirred overnight. The mixture was cooled to 0 °C and quenched with 2 M aqueous HCl (440 mL). The organic phase was separated and the aqueous phase extracted three times with diethyl ether (3 × 200 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness to give crude 2-methyl-2-carboethoxy-1-tetralone (19.5 g, 92% yield). GC (80 °C, 2 min, 20 °C/min, 300 °C, 4 min, inj. 260 °C, det. 260°, flow 1.5 mL/min): rt 9.9 min. GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min): rt 9.2 min. EI-MS: 232 (39, M^+), 217 (7, M^+−Me), 187 (5, M^+−OEt), 158 (100, M^+−COOEt), 131 (19), 118 (46), 90 (29). ^{1}H NMR (500 MHz, $CDCl_3$):1.15 (t, $J = 7.1$ Hz, CH_3CH_2, 3H), 1.49 (s, Me–C(2), 3H), 2.00–2.06 (m, H–C(3), 1H), 2.54–2.62 (m, H–C(3), 1H), 2.90–3.06 (m, H–C(4), 2H), 4.12 (qd, $J = 1.9$, 7.1 Hz, OCH_2, 2H), 7.20 (d, 7.7 Hz, H–C(5), 1H), 7.29 (dd, $J = 7.5$, 7.7 Hz, H–C(6), 1H), 7.45 (dd, $J = 1.4$, 7.5 Hz, H–C(7), 1H), 8.05 (dd, $J = 1.4$, 7.9 Hz, H–C(8), 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): 14.0 (q, CH_3CH_2), 20.6 (q, Me–C(2)), 26.0 (t, C(3)), 33.9 (t, C(4)), 53.8 (s, C(2)), 61.2 (t, CH_2CH_3), 126.7 (d, C(6)), 128.0 (d, C(8)), 128.7 (d, C(5)), 131.8 (s, C(4a)), 133.4 (d, C(7)), 143.1 (s, C(8a)), 172.8 (s, COOEt), 196.1 (s, C(1)).

4.3.3. 2-Methyl-1-tetralone-2-carboxylic acid benzyl ester 1 (from 9). Benzyl ester **1** was prepared by transesterification with benzyl alcohol in the presence of tetraisopropyl titanate, as described by Seebach et al.[19] To a mixture of **8** (10 g, 43 mmol) and benzyl alcohol (37 mL, 357 mmol) was added titanium isopropoxide (12.8 mL, 43.3 mmol) and the mixture heated at 120 °C for 3 h. The cooled mixture (<20 °C) was quenched with 1 M HCl and extracted with ether/hexane (1:1). The organic extract was washed with saturated aqueous solution of $NaHCO_3$ and saturated NaCl solution, and dried with $MgSO_4$. The solvent was distilled off (65–75 °C/0.05–0.1 torr) and the residue was purified by flash chromatography (petrol ether/acetone, 9:1) to give 7.1 g (56% yield) racemic benzyl 2-methyl-1-tetralone-2-carboxylate. GC (80 °C, 2 min, 20 °C/min, 300 °C, 4 min, inj. 260 °C, det. 260°, flow 1.5 mL/min): rt 12.9 min. GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min): rt 13.1 min. EI-MS: 294 (14, M^+), 203 (10, M^+−Bn), 159 (51, M^+−COOBn), 145 (7), 141 (9), 131 (16), 118 (31), 91 (100), 65 (11). HPLC (9:1 *n*-hexane/2-propanol, flow 0.9 mL/min): rt 13.3 and 14.5 min, (*R*)- and (*S*)-enantiomers of **1** (1:1, not assigned). ^{1}H NMR (500 MHz, $CDCl_3$): 1.52 (s, Me–C(2), 3H), 2.02–2.08 (m, H–C(3), 1H), 2.57–2.62 (m, H–C(3), 1H), 2.78–2.99 (m, H–C(4), 2H), 5.05 (d, 12.5 Hz, OCH_2, 1H), 5.17 (d, 12.5 Hz, OCH_2, 1H), 7.10–7.14 (m, 2H), 7.17 (d, $J = 7.7$ Hz, 1H), 7.23–7.25 (m, 3H), 7.29–7.32 (m, 1H), 7.43–7.47 (dd, $J = 1.4$, 6.5 Hz, H–C(7), 1H), 8.06 (dd, $J = 1.1$, 7.9 Hz, H–C(8), 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.5 (q, Me), 25.9 (t, C(3)), 33.9 (t, C(4)), 53.9 (s, C(2)), 66.7 (t, CH_2Ph), 126.8 (d, Ph), 127.6 (2d, Ph), 128.0 (d, C(5)), 128.0 (d, C(6)), 128.4 (2d, Ph), 128.7 (d, C(7)), 131.9 (s, Ph), 133.4 (d, C(8)), 135.6 (s, C(4a)), 143.1 (s, C(8a)), 172.8 (s, COO), 196.1 (s, C(1)). Anal. Calcd for $C_{19}H_{18}O_3$ (294.35): C, 77.53; H, 6.16; O, 16.31. Found: C, 77.44; H, 6.26; O, 16.39.

4.3.4. 2-Methyl-1-tetralone-2-carboxylic acid 2. 2-Methyl-2-carbomethoxy-1-tetralone (17.4 g, 80 mmol), prepared by acylation of 1-tetralone with dimethyl carbonate and methylation with MeI in the presence of *t*-BuOK by the methods described above, was dissolved in methanol (250 mL) and cooled down to 0 °C on an ice-water bath. A pre-cooled aqueous solution of KOH (13.5 g in 110 mL water) was slowly poured into the methanolic solution of 2-methyl-2-carbomethoxy-1-tetralone and the mixture was led to warm up to room temperature and stirred for 2 h. Methanol was evaporated under reduced pressure at 0 °C. The aqueous-methanolic phase was extracted with dichloromethane (5×40 mL), acidified with diluted HCl to pH 2 and again extracted with dichloromethane (5×50 mL). The organic extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated to 1/3 and the product was then crystallized by adding a portion of hexane. The mother liquor was concentrated in vacuum and the pure white crystals of 2-carboxy-2-methyl-1-tetralone (11.6 g, 71% yield) were separated by filtration. The acid was unstable at room temperature and decomposed readily to the 2-methyl-1-tetralone and carbon dioxide (see also Ref. 8). Therefore, it was stored in the freezer at −20 °C, where it remained stable for a period of weeks. TLC: R_f 0. ^1H NMR (500 MHz, $CDCl_3$):1.41 (s, Me–C(2), 3H), 1.98–2.03 (m, H–C(3), 1H), 2.45–2.49 (m, H–C(3), 1H), 2.82–2.88 (m, H–C(4), 1H), 2.95–3.01 (m, H–C(4), 1H), 7.12 (d, $J = 7.7$ Hz, H–C(5), 1H), 7.20 (dd, $J = 7.4$, 7.7 Hz, H–C(7), 1H), 7.37 (ddd, $J = 1.1$, 7.4, 7.8 Hz, H–C(6), 1H), 7.94 (d, $J = 7.8$ Hz, H–C(8), 1H), 12.75 (br s, OH, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.4 (q, Me–C(2)), 25.6 (t, C(3)), 33.2 (t, C(4)), 53.4 (s, C(2)), 126.8 (d, C(6)), 128.0 (d, C(8)), 128.7 (d, C(5)), 131.8 (s, C(4a)), 133.7 (d, C(7)), 143.2 (s, C(8a)), 178.7 (s, COOH), 196.2 (s, C(1)).

4.3.5. 2-Methyl-1-tetralone 3. TLC: R_f 0.50. GC (80 °C, 2 min, 20 °C/min, 300 °C, 4 min, inj. 260 °C, det. 260°, flow 1.5 mL/min): rt 8.2 min. GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min): rt 7.5 min. EI-MS: 160 (72), 145 (28), 131 (22), 118 (100), 90 (50), 77 (10), 63 (8), 51 (7), 39 (6). HPLC (9:1 *n*-hexane/2-propanol, flow 0.9 mL/min): 7.2 min (*R*)-**4** and 7.8 min (*S*)-**4**. The absolute configuration was determined by comparison with published data.[20] ^1H NMR (500 MHz, $CDCl_3$):1.25 (d, $J = 6.8$ Hz, Me–C(2), 3H), 1.82–1.90 (m, H–C(2), 1H), 2.15–2.20 (m, H–C(3), 1H), 2.55–2.59 (m, H–C(3), 1H), 2.92–3.05 (m, H–C(4), 2H), 7.21 (d, $J = 7.7$ Hz, H–C(5), 1H), 7.27 (dd, $J = 7.4$, 7.7 Hz, H–C(7), 1H), 7.43 (dd, $J = 7.4$, 7.8 Hz, H–C(6), 1H), 8.01 (d, 7.8 Hz, H–C(8), 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 15.2 (q, Me–C(2)), 28.6 (t, C(3)), 31.1 (t, C(4)), 42.4 (d, C(2)), 126.3 (d, C(6)), 127.0 (d, C(8)), 128.5 (d, C(5)), 132.1 (s, C(4a)), 133.9 (d, C(7)), 144.0 (s, C(8a)), 200.5 (s, C(1)). Anal. Calcd for $C_{11}H_{12}O$ (160.22): C, 82.46; H, 7.55; O, 9.99. Found: C, 82.44; H, 7.47; O, 10.03.

4.3.6. 2-Methyl-1-indanone-2-carboxylic acid benzyl ester 4. Benzyl ester **4** was prepared from 1-indanone by the same procedure as benzyl ester **1**. The total yield of acylation, methylation, and transesterification was 36%. GC (80 °C, 2 min, 20 °C/min, 300 °C, 4 min, inj. 260 °C, det. 260°, flow 1.5 mL/min): rt 12.1 min. GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min): rt 12.5 min. EI-MS: 280 (4, M^+), 189 (7, M^+−Bn), 146 (75, M^+−COOBn), 133 (14), 115 (31), 105 (3), 91 (100), 77 (8), 65 (14), 51 (5). HPLC (9:1 *n*-hexane/2-propanol, flow 0.9 mL/min): rt 18.1 and 21.4 min, (*R*)- and (*S*)-enantiomers of **4** (1:1, not assigned). ^1H NMR (500 MHz, $CDCl_3$): 1.54 (s, Me–C(2), 3H), 2.99 (d, $J = 17.1$ Hz, H–C(3), 1H), 3.69 (d, $J = 17.1$ Hz, H–C(3), 1H), 5.10 (d, 12.6 Hz, OCH_2, 1H), 5.15 (d, 12.6 Hz, OCH_2, 1H), 7.13–7.33 (m, 5H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.60 (dd, $J = 1.1$, 7.5 Hz, H–C(7), 1H), 7.78 (dd, $J = 1.1$, 7.7 Hz, H–C(8), 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 21.0 (q, Me), 39.9 (t, C(3)), 56.1 (s, C(2)), 66.9 (t, $\mathit{C}H_2Ph$), 126.5 (d, Ph), 127.7 (2d, Ph), 128.0 (d, C(5)), 128.2 (d, C(6)), 128.5 (2d, Ph), 129.0 (d, C(7)), 134.7 (s, Ph), 135.3 (d, C(8)), 135.7 (s, C(4a)), 152.5 (s, C(8a)), 171.8 (s, COO), 203.2 (s, C(1)). Anal. Calcd for $C_{18}H_{16}O_3$ (280.33): C, 77.12; H, 5.75; O, 17.12. Found: C, 77.33; H, 6.21; O, 16.89.

4.3.7. 2-Methyl-1-indanone 5. GC (80 °C, 2 min, 20 °C/min, 300 °C, 4 min, inj. 260 °C, det. 260°, flow 1.5 mL/min): rt 7.2 min. GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min): rt 6.9 min. EI-MS: 146 (69), 131 (100), 117 (33), 103 (26), 91 (14), 77 (11), 63 (9), 51 (13), 39 (11). HPLC (9:1 *n*-hexane/2-propanol, flow 0.9 mL/min): 8.5 min (*R*)-**5** and 9.2 min (*S*)-**5**. The absolute configuration was determined by comparison with published data.[20]

4.3.8. 1,3,3-Trimethyl-2-oxo-cyclohexanecarboxylic acid benzyl ester 6. The benzyl ester **6** was prepared by transesterification with tetraisopropyl titanate as described by Seebach et al.[19] To a mixture of 1,3,3-trimethyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (1.16 g, 5.5 mmol) and benzyl alcohol (8 mL, 77 mmol) was added titanium isopropoxide (1.7 mL, 5.8 mmol) and the mixture was heated at 120 °C for 3 h. The cooled mixture (<20 °C) was quenched with 1 M HCl (20 mL) and extracted with ether/hexane (1:1). The organic extract was washed with a saturated aqueous solution of sodium hydrogen carbonate and saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was distilled off (65–75 °C/0.05–0.1 torr) and the residue purified by flash chromatography (hexane/ethyl acetate, 9:1) to give 0.82 g (54% yield) racemic **6**. GC (80 °C, 2 min, 10 °C/min, 180 °C, 20 min, inj. 200 °C, det. 200 °C, flow 1.5 mL/min, CP-Chirasil-Dex CB ($25\,m \times 0.25\,mm \times 0.25\,\mu m$)): rt 19.1 min and 19.3 min, (*R*)- and (*S*)-enantiomers of **6** (1:1, not assigned). GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min, HP-5MS (30 m, 0.25 mm, 0.25 μm)): rt 11.7 min. EI-MS: 274 (5, M^+), 177 (6), 155 (11), 140 (42), 125 (5), 109 (17), 91 (100), 69 (19), 55 (8). ^1H NMR (500 MHz, $CDCl_3$): 0.97 (s, CH_3, 3H), 1.07 (s, CH_3, 3H), 1.31 (s, CH_3, 3H), 1.39–1.46 (m, CH_2, 1H), 1.56–1.62 (m, CH_2, 2H), 1.66–1.70 (m, CH_2, 1H), 1.95–

1.99 (m, CH_2, 1H), 2.52–2.57 (m, CH_2, 1H), 5.04 (d, $J = 12.39$ Hz, CH_2Ph, 1H), 5.17 (d, $J = 12.39$ Hz, CH_2Ph, 1H), 7.28–7.41 (m, Ph, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): 18.4 (t), 23.5 (q), 25.3 (q), 26.7 (q), 36.8 (t), 40.5 (t), 46.0 (s), 55.2 (s), 66.7 (t, CH_2Ph), 128.1 (2d), 128.2 (d), 128.5 (2d), 135.2 (s), 172.5 (s, C=O ester), 211.3 (s, C=O oxo). Anal. Calcd for $C_{17}H_{22}O_3$ (274.36): C, 74.42; H, 8.08; O, 17.49. Found: C, 74.51; H, 8.12; O, 17.34.

4.3.9. 2,2,6-Trimethylcyclohexanone 7. Product of decarboxylation of **6**. GC (80 °C, 2 min, 10 °C/min, 180 °C, 20 min, inj. 200 °C, det. 200 °C, flow 1.5 mL/min, CP-Chirasil-Dex CB (25 m × 0.25 mm × 0.25 µm)): rt 6.6 min (*R*)-**7** and 6.8 min (*S*)-**7**. The absolute configuration was determined by comparison with published data.[21,22] GC–MS (80 °C, 2 min, 20 °C/min, 280 °C, 8 min, inj. 250 °C, flow 1 mL/min, HP-5MS (30 m, 0.25 mm, 0.25 µm)): rt 4.7 min. EI-MS: 140 (22, M^+), 97 (10), 82 (100), 69 (48), 56 (49), 41 (40), 39 (20).

4.4. Typical decarboxylation procedure

Starting from **1**: the experiments were carried out in a 50-mL glass reactor equipped with heating and magnetic stirring. The catalyst (5 wt % Pd/C, Fluka) and the chiral amino alcohol (0.3 equiv to substrate) were brought into the reactor together with the solvent (acetonitrile, 5 mL), then 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 the addition of **1** (100 mg, 0.34 mmol), dissolved in acetonitrile (5 mL), via a syringe under hydrogen atmosphere. The samples withdrawn during the reaction were filtered and analyzed using GC, chiral HPLC, and GC–MS.

Starting from **2**: the chiral amino alcohol (1 equiv to substrate) and the solvent (acetonitrile, 4 mL) were stirred magnetically in a 25 mL round-bottomed flask under an argon atmosphere at room temperature. The reaction was started by the addition of acid **2** (40 mg, 0.2 mmol) dissolved in 1 mL acetonitrile via a syringe under an argon atmosphere. To the samples withdrawn during the reaction, an excess of etheric diazomethane solution was added to quench the reaction before chromatography. Thus, the unreacted acid **2** was immediately and completely transformed to its methyl ester.

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