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Research Note

Enantioselective hydrogenation of arecaidine over cinchona alkaloid-modified palladium catalyst: A novel route to enantioenriched nipecotic acid derivatives

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ABSTRACT

The hydrogenation of *N*-methyl-3,4-dehydronipecotic acid (arecaidine) over Pd/Al_2O_3 catalyst in presence of cinchona alkaloids and benzylamine additive results in the quantitative formation of *N*-methylnipecotic acid in good (up to 60%) optical purity. The reaction is a novel example of the efficient use of chirally modified heterogeneous metal catalysts allowing the preparation of enantioenriched *N*-heterocyclic carboxylic acids.

1. Introduction

The biological activity of natural *N*-heterocyclic compounds is the driving force behind efforts aimed at developing novel asymmetric synthetic methods for the preparation of the substructures of these pharmacologically active substances [1]. Several methods, including asymmetric catalytic procedures, have been elaborated for the synthesis of these optically pure building blocks [2,3]. Among these, the asymmetric catalytic hydrogenation of substituted unsaturated *N*-heterocycles has proven to be a convenient method [4–6]. Due to the advantages of the heterogeneous catalysts, the preparation of saturated *N*-heterocycles by asymmetric hydrogenation over such catalysts also has been attempted [7]. The most successful strategies used the diastereoselective hydrogenation of the aromatic heterocyclic compounds coupled with optically pure auxiliaries [8,9]. The direct enantioselective hydrogenation of the *N*-heterocyclic substrates over chiral heterogeneous catalysts should be a more convenient procedure. To date, only a few efficient heterogeneous chirally modified catalysts have been developed for the hydrogenation of β-keto esters, activated ketones, 2-pyrone derivatives, and prochiral α,β-unsaturated carboxylic acids [10–16].

The hydrogenation of α,β-unsaturated carboxylic acids of diverse structures over supported Pd catalysts in the presence of cinchona alkaloids provides saturated carboxylic acids in good to excellent optical purities [17–30]. The hydrogenation of the unsaturated esters results in a loss of enantiodifferentiation compared with the corresponding free carboxylic acids [17,20,28]. Attempts at the enantioselective hydrogenation of *N*-containing acids or esters over modified metal catalysts have resulted in low optical purity [31–36]; only fair enantioselectivity was reported recently over cinchona-Pd catalyst [37]. The hydrogenation of an *N*-heterocyclic ester in this catalytic system also gave disappointing results; even under harsh reaction conditions, the hydrogenation of ethyl 1,4,5,6-tetrahydronicotinate produced 24% enantioselectivity accompanied by low yield over cinchona-modified Pd [38]. Similarly, low enantioselectivity has been obtained in the one-step hydrogenation of ethyl nicotinate to ethyl nipecotinate over a chiral Pd complex immobilized in the pores of mesoporous silica [39]. The heterogeneous enantioselective hydrogenation of C=N group has proven even more difficult, and thus is not considered a viable alternative for the preparation of optically enriched *N*-heterocyclic carboxylic acid derivatives [40,41].

In the present study, we used a novel strategy to prepare optically enriched nipecotic acid derivatives by heterogeneous catalytic hydrogenation over cinchona-modified Pd catalyst. Based on previous findings (e.g., hydrogenation of free carboxylic acids in higher optical yields as the corresponding esters [17,20], sluggish hydrogenation of the substrate containing a secondary amino group [38]), we designed the structure of the *N*-heterocyclic α,β-un-

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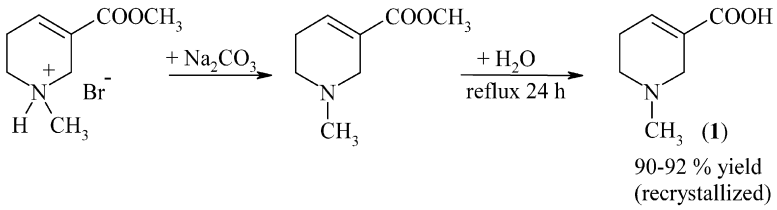


Scheme 1. Preparation of arecaidine (**1**) from arecoline hydrobromide [44].

saturated carboxylic acid to increase the enantioselectivity of hydrogenation in the presence of cinchona alkaloids.

2. Experimental

The 5% Pd/Al_2O_3 (Engelhard 40692) commercial catalyst (metal dispersion, 0.19–0.21; BET surface area, 185–200 $m^2\,g^{-1}$; average Pd particle size, 5.8 nm) [18,42,43], arecoline hydrobromide, and the cinchona alkaloids, solvents, and reagents (Aldrich and Fluka products) were used as received. Arecaidine (**1**) was prepared as described previously [44], as shown in Scheme 1. Hydrogenations were performed in a glass hydrogenation apparatus or a glass-lined stainless steel autoclave. The catalyst and solvent were loaded into the reactor and stirred at 1000 rpm for 30 min under H_2, followed by addition of the modifier, stirring for another 5 min, and then addition of **1** and benzylamine (BA). The reactor was flushed with H_2 and pressurized to the desired pressure, and the mixture was stirred (1000 rpm) while the H_2 uptake was recorded. H_2 consumption of up to 20% of the total uptake was used to calculate the initial reaction rate (R_i). After the specified reaction time, the catalyst was removed by filtration, the solution was neutralized using HCl ethanolic solution, and the products were analyzed by gas chromatograph (Agilent Techn. 6890N GC–5973 MSD and HP 5890 ser II GC–FID) with a Cyclosil-B (30 m × 0.2 mm, J&W Scientific) chiral capillary column. Analysis of samples transformed in methyl esters using CH_2N_2 ethereal solution gave identical results to those for the free carboxylic acid samples. The *N*-methylnipecotic acid (**2**) enantiomers were identified after transformation in methyl esters and comparison of retention time with that of a sample prepared from commercial (*S*)-nipecotic acid by reaction with methyliodide. The enantioselectivity was expressed as enantiomeric excess (ee), calculated as

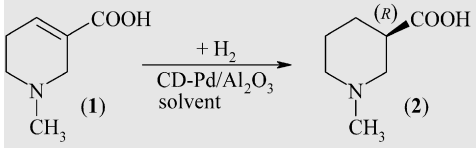
$$\text{ee}\ (\%) = \left|\left[(R)-\mathbf{2}\right]-\left[(S)-\mathbf{2}\right]\right| \times 100/\left(\left[(R)-\mathbf{2}\right]+\left[(S)-\mathbf{2}\right]\right).$$

3. Results and discussion

According to earlier results on the enantioselective hydrogenation of prochiral α,β-unsaturated carboxylic acids and esters [17,20], the presence of a free carboxylic acid group leads to increased enantioselectivity. In addition, a secondary amine group in the β position has a detrimental effect, likely due to its competition with the quinuclidine *N* of the modifier in the interaction with the carboxyl group and also its deactivation effect, as demonstrated by the hydrogenation of ethyl 1,4,5,6-tetrahydronicotinate [38]. The possible intermolecular and intramolecular side reactions of this group also may contribute, as indicated by the difficulty preparing 1,4,5,6-tetrahydronicotinic acid. Thus, changing the position of the C=C double bond and *N*-alkylation of the secondary amino group was expected to have a beneficial effect on the rate and selectivity of hydrogenation. Based on the foregoing considerations, we investigated the hydrogenation of *N*-methyl-1,2,5,6-tetrahydronicotinic acid (**1**) prepared by hydrolysis of commercially available arecoline (see Scheme 1).

The hydrogenation of **1** resulted in selective formation of *N*-methyl nipecotic acid (**2**), rapidly reaching complete conversion

Table 1
Enantioselective hydrogenation of **1** over CD modified Pd catalysts[a]

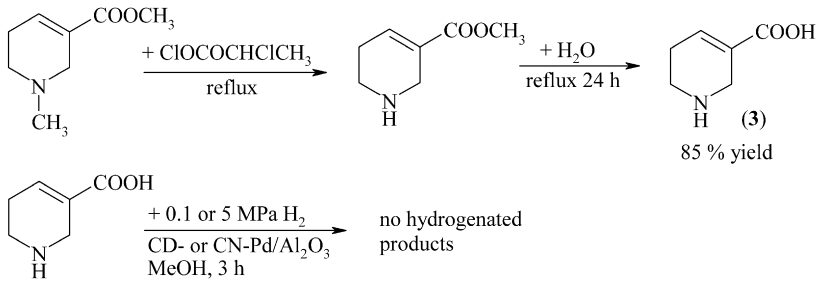


Entry	Solvent	Additive[b]	Time[c] (min)	R_i ($mmol\,g_{cat}^{-1}\,h^{-1}$)	ee (%)
1[d]	MeOH	–	10	115	–
2	MeOH	–	25	59	18
3[e]	MeOH	–	30	33	33
4	MeOH	BA	15	73	39
5[f]	MeOH	BA	35	36	40
6[g]	MeOH	BA	80	13	40
7[h]	MeOH	BA	50	33	32
8	EtOH	BA	20	62	30
9[e]	H_2O	–	110	38	0
10	AcOH	–	40	32	10
11	DMF[i]	BA	20	67	20

[a] Reaction conditions: 50 mg Pd/Al_2O_3, 3 ml solvent, 0.7 mmol **1**, 0.035 mmol CD, 0.1 MPa H_2, stirring 1000 rpm, 295 ± 2 K.
[b] Additive: 0.7 mmol BA.
[c] Reaction time needed for complete conversion.
[d] Reaction without modifier.
[e] Using 0.35 mmol CD.
[f] Over catalyst pretreated in flow of H_2 at 523 K.
[g] Reaction carried out at 274 ± 2 K.
[h] Over 5% Pd/TiO_2 catalyst prepared by precipitation.
[i] *N*,*N*-dimethylformamide with 2.5 vol% water content.

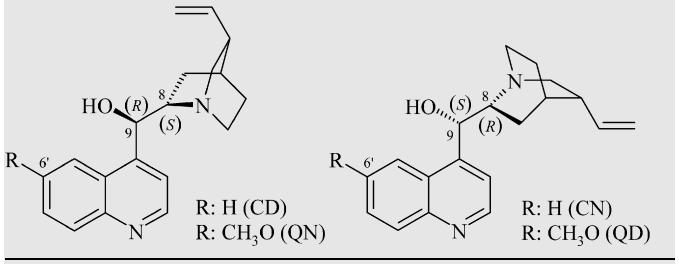
even under low H_2 pressure (see Table 1). In the presence of 5 mol% cinchonidine (CD; CD/Pd_{surf} molar ratio about 7.5) in MeOH, the R_i decreased by half compared with the racemic reaction; however, even in the presence of the modifier, **1** was hydrogenated in less than 30 min. Low ee in favor of the (*R*)-**2** enantiomer was obtained, which was increased by using 50 mol% CD. The addition of achiral organic base to the reaction mixture is known to have a beneficial effect on the ee in the hydrogenation of α,β-unsaturated carboxylic acids of various structures [21,24–30,36,37]. Using benzylamine (BA) as an additive in the hydrogenation of **1** resulted in a significant increase in ee, accompanied by an increase in R_i, similar to that observed in the hydrogenation of α-phenylcinnamic acid and its methoxy-substituted derivatives [21,25,26]. The reaction was free of external diffusion control, as verified by using various catalyst amounts and stirring velocities (data not shown). Thus, we can conjecture that BA may act similarly as in the hydrogenation of α-phenylcinnamic acid, increasing the desorption rate of the strongly adsorbed *N*-containing saturated acid interacting with the modifier on the Pd surface. This interpretation requires confirmation by further studies; however. Similar ee values were obtained over the catalyst prereduced in a flow of H_2 at 523 K and also in the reaction carried out at 274 K, whereas R_i was significantly decreased in both reactions. No increases in ee were achieved by changing the catalyst to 5% Pd/TiO_2 or by hydrogenation in other solvents, as shown in Table 1.

Further increases in both R_i and ee were attained by increasing the H_2 pressure (see Table 2); however, unlike in the hydrogena-



Scheme 2. Preparation [48] and attempts on enantioselective hydrogenation of guvacine (**3**) over cinchona modified Pd catalyst.

Table 2
H_2 pressure and modifier structure effect on the enantioselective hydrogenation of **1** over cinchona modified Pd/Al_2O_3 catalyst[a]



Entry	Modifier	pH_2 (MPa)	Time[b] (min)	R_i (mmol g_{cat}^{-1} h^{-1})	ee (%) (Conf.)[c]
1	CD	0.1	15	73	39 (*R*)
2	CD	1	8	129	43 (*R*)
3	CD	2	5	180	47 (*R*)
4[d]	CD	2	5	171	50 (*R*)
5	CD	3	5	256	45 (*R*)
6	CD	5	5	316	44 (*R*)
7	CD	10	5	n.d.[e]	37 (*R*)
8	QN	2	10	156	5 (*R*)
9	CN	2	5	177	50 (*S*)
10[d]	CN	2	5	169	60 (*S*)
11	QD	2	5	183	16 (*S*)

[a] Reaction conditions: 50 mg Pd/Al_2O_3, 3 ml MeOH, 0.7 mmol **1**, 0.035 mmol modifier, 0.7 mmol BA, stirring 1000 rpm, 295 ± 2 K.
[b] Reaction time needed for complete conversion.
[c] Configuration of the excess enantiomer.
[d] Using 0.07 mmol CD.
[e] n.d.—not determined.

tion of prochiral α,β-unsaturated aliphatic carboxylic acids [18] and α-acetamidoacrylic acid [37], here the ee achieved maximal value under 2 MPa H_2 pressure, resembling the recently reported behavior in the hydrogenation of itaconic acid [28]. The ee was further increased up to 50% by increasing the amount of CD to 10 mol% (with respect to **1**). The high amount of CD used to obtain the best ee indicates that a relatively high concentration of dissolved CD-acid salt (either dimer or monomer acid) is needed to obtaining good ee in this system, as is typically the case in the hydrogenation of α,β-unsaturated aliphatic carboxylic acids [45]. We assume that this may be related to the adsorption strengths of CD, **1**, and CD-**1** salt and also to the possible reactions between the dissolved CD-**1** salt and the adsorbed modifier, similar to a previous proposal [46].

Interestingly, the use of cinchonine (CN) resulted in higher ee values compared with CD, along with inversion of the ee sense corresponding to the opposite configuration of the C^8 and C^9 chiral centers of the modifier. Thus, (*S*)-**2** was obtained at up to 60% optical purity using 10 mol% CN. This observation is rather surprising; generally, the use of CN instead of CD results in significantly lower ee in the hydrogenation of prochiral α,β-unsaturated carboxylic acids over Pd catalysts [28,45,47]. Similar behavior was observed only in the hydrogenation of α-acetamidoacrylic acid, another *N*-containing compound [37]. Methoxy substituent on the $C^{6'}$ of the quinoline moiety decreased the ee substantially in both series of cinchona alkaloids, however, in this pair, also the (*R*)C^8–(*S*)C^9 cinchona (quinidine) gave a higher ee value than quinine.

Finally, the strategy used in this work seems to give good results for the preparation of optically enriched *N*-methyl nipecotic acid by enantioselective heterogeneous catalytic hydrogenation of the corresponding α,β-unsaturated acid. An essential feature of the substrate design is the use of a compound bearing tertiary *N*. The importance of this factor was verified by attempting the hydrogenation of guvacine (**3**) prepared according to Scheme 2 [48]. No hydrogenation products were detected under H_2 pressure of 0.1 or 5 MPa over either CD- or CN-modified Pd/Al_2O_3 after 3 h of reaction, thus confirming our rationale.

In conclusion, in the present study we have extended the applicability of the cinchona alkaloid-modified Pd catalyst on the enantioselective hydrogenation of a tetrahydronicotinic acid derivative through careful choice of the structural elements of the substrate. The proper position of the C=C group, the presence of a free carboxylic acid group, and alkylation of the *N* are the key features that together result in the enantioselective formation of the saturated product. This is the first reported example of hydrogenation of an *N*-heterocyclic α,β-unsaturated carboxylic acid over a chirally modified supported noble metal catalyst with satisfactory optical purity. Obviously, gaining more insight into the influence of the reaction parameters on the rate and enantioselectivity of the reaction and elucidating the structure of the surface intermediate responsible for enantioselection require further detailed kinetic, spectroscopic, and theoretical studies, which will be the subject of our future investigations. As it stands, however, the pharmaceutical importance of the chiral piperidine derivatives makes this approach an interesting and novel preparation procedure, the further development of which may eventually result in practical applications.

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