Enantioselective hydrogenation of citral using modified SCILL catalysts as a key step for the synthesis of (-)-menthol

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ABSTRACT

The enantioselective hydrogenation of citral to (+)-citronellal is a key intermediate step in the synthesis of the valuable aroma compound (-)-menthol. In this study we developed a system based on a modified SCILL catalyst that allows this reaction. The chiral modifier (R)-(+)-2-(Diphenylmethyl)pyrrolidine and trifluoroacetic acid were dissolved in the Ionic Liquid [BMIM][BF_4] and coated as a thin layer on a Pd catalyst (d_{Pd} = 2.5 nm). In the first step the role of each of the participating components was systematically evaluated. Only the combination of (R)-(+)-2-(Diphenylmethyl)pyrrolidine and trifluoroacetic acid leads to an enantiomeric excess, which can be further improved by the fixation of the modifier and trifluoroacetic acid on the catalyst *via* an Ionic Liquid. In a second step the effect of different reaction conditions (temperature, pressure and solvent) were investigated. The enantiomeric excess of (+)-citronellal was significantly increased by reducing the reaction pressure and using toluene as solvent, reaching a value of 61%, and (±)-citronellal was obtained at a yield of 76%.

KEYWORDS: citral, citronellal, enantioselective hydrogenation, SCILL catalyst

ABBREVIATIONS

CIT, citral; CAL, citronellal; DMP, (R)-(+)-2-(Diphenylmethyl)pyrrolidine; TFA, trifluoroacetic
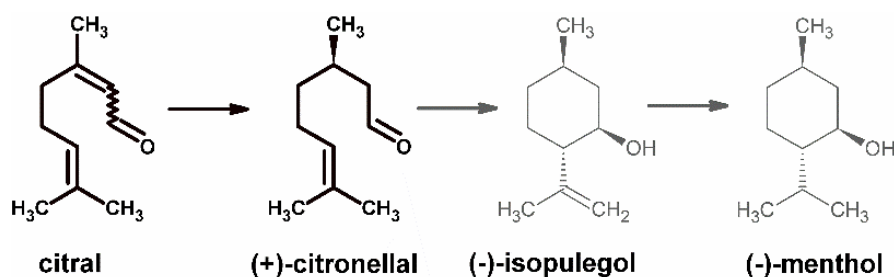
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acid; IL, Ionic Liquid; [BMIM][BF_4], 1-Butyl-3-methylimidazolium tetrafluoroborate; ee, enantiomeric excess; X, conversion; S, selectivity; Y, yield.

INTRODUCTION

Due to its characteristic odour and strong cooling effect, (-)-menthol is used in many products, for example in toothpastes, pharmaceuticals, tobacco, cosmetics, confectioneries, chewing gum, etc. Menthol has four stereoisomeric pairs, but only (-)-menthol has the characteristic odour and strong cooling effect [1, 2]. Therefore its enantiomer (+)-menthol as well as the other diastereomeres (±)-neo-menthol, (±)-iso-menthol and (±)-neoiso-menthol are of lesser value. A large fraction of the menthol produced is obtained by extraction from natural sources. Synthetic routes for the production of (-)-menthol are based on an enantioselective crystallization process (Harrmann-Reimer process) or on a chiral homogenous catalyst (Takasago and BASF process) [2, 3]. Considering the disadvantages of the latter due to higher prices and challenges in the reuse of the catalyst, the use of heterogeneous catalysts would be an attractive alternative. An enantioselective hydrogenation of citral (CIT) to (+)-citronellal ((+)-CAL) can be the first step of a heterogeneous route to (-)-menthol. The (+)-CAL obtained can be cyclized in a second step to (-)-isopulegol, which can then be hydrogenated to (-)-menthol in the final step (Figure 1).

An enantioselective hydrogenation of citral was realized using a dual catalyst system consisting of Pd/$BaSO_4$ in combination with trifluoroacetic acid and 2-diarylmethylpyrrolidines as chiral modifier

Figure 1. Simplified reaction network of the transformation of citral to menthol.
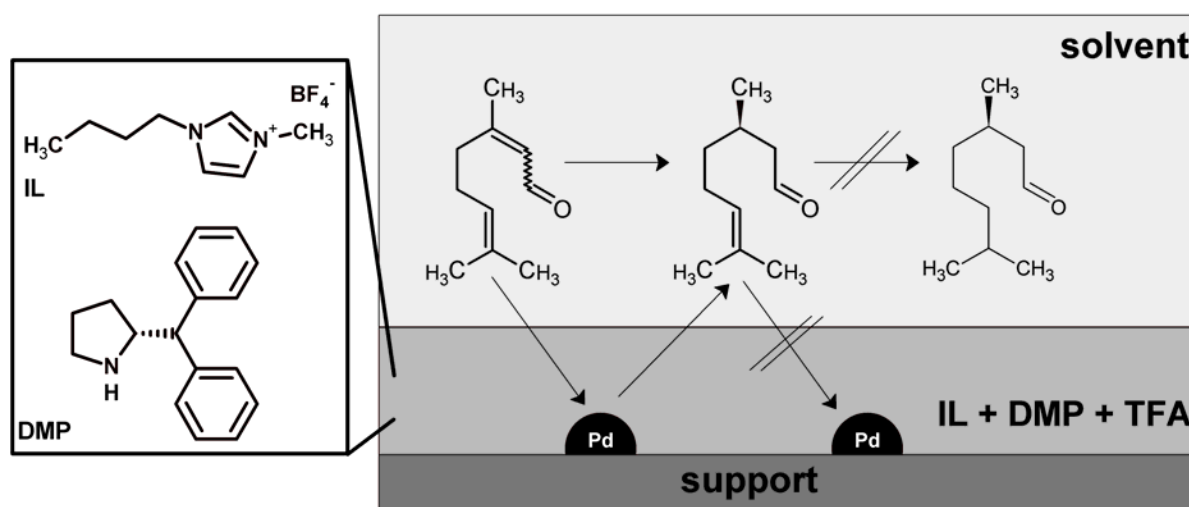
Figure 2. Assumed structure of an IL-coated solid catalyst modified with DMP and TFA.

in a mixture of t-BuOH/H$_2$O. Using (R)-(+)-2-(Diphenylmethyl)pyrrolidine an overall yield of 65% for (±)-CAL and an enantiomeric excess (ee) of 77% for (+)-CAL was obtained after a reaction time of 21 hours [4, 5]. The ee was increased to 89% by a modification of the aryl group. The authors suggest a mechanism based on the initial formation of an iminium cation from CIT and 2-diarylmethylpyrrolides, which is rapidly shifted to a sterically more stable E-iminium species, leading to an enantiomeric excess in a further hydrogenation step [5]. The presence of Pd leads to a selective hydrogenation of the conjugated double bond forming CAL [6]. However, a consecutive hydrogenation of the isolated double bond forming dihydrocitronellal results in a reduced CAL yield [4, 5]. The consecutive hydrogenation of citronellal was avoided by using a SCILL catalyst (solid catalyst with ionic liquid layer), thereby achieving

a yield of > 99% for (±)-CAL [7-11]. In the combined second and third step of the transformation of citral to menthols, yields of > 90% for menthols including (±)-menthol, (±)-neo-menthol, (±)-iso-menthol and (±)-neoiso-menthol) can be achieved using heterogeneous metal/H-BEA catalysts, for example Pt/H-BEA [12], Ir/H-BEA [13, 14] and, as shown by our group, Ru/H-BEA [15, 16]. The aim of this study was to combine the concepts of the formation of highly selective as well as enantioselective (+)-CAL in one heterogeneous catalyst system. Hence, we coated a heterogeneous Pd/SiO$_2$ nanocatalyst (Pd particle size = 2.5 nm) with an Ionic Liquid (IL, [BMIM][BF$_4$]), (R)-(+)-2-(Diphenylmethyl)-pyrrolidine (DMP) and trifluoroacetic acid (TFA). An assumed structure of an IL-coated solid catalyst modified with DMP and TFA is shown in figure 2. According to Arras *et al.* [7] DMP and TFA are dissolved in the IL

and coated on the catalytically active metal nanoparticles.

MATERIALS AND METHODS

Preparation of IL-coated catalysts

The Pd/SiO$_2$ catalyst has been described elsewhere [17]. In brief, its main characteristics are: Pd loading = 1 wt.%, Pd particle size d_{Pd} = 2.5 nm and specific surface area according to Brunauer–Emmett–Teller (BET) [18] = 216 m^2 g^{-1}. 0.25 g IL, 0.25 g DMP and 0.1 ml TFA were dissolved in acetone and impregnated on 0.5 g Pd/SiO$_2$. After drying at 373 K, the catalyst was used without any further treatment. The pore filling degree α_{IL} is defined as the ratio of the IL volume V_{IL} and the catalyst's total pore volume $V_{pore,total}$ [19].

$$\alpha_{IL} \ (\%) = (V_{IL}/V_{pore,total}) \cdot 100 \qquad (1)$$

For the obtained catalysts the pore filling degree α_{IL} is 55%.

Hydrogenation experiments

The hydrogenation of citral (10 mL, Merck) was carried out in a batch vessel (Parr Co., 300 mL) at 353 K and 20 bar hydrogen pressure, unless otherwise stated, using 150 mL solvent (unless otherwise stated n-hexane was used) and n-dodecan as internal standard. Samples were taken periodically and analysed via gas chromatography (Shimadzu GC 2010; 343 K, 1 min; 1 K min^{-1} → 383 K; 4 K min^{-1} → 453 K, 5 min) using a chiral HYDRODEX ß-TBDAc column (Macherey-Nagel). Conversion (X) and selectivities (S$_i$) were calculated via the following equations.

$$X_{CIT} \ (\%) = (1-(c_{CIT}/c_{CIT,0})) \cdot 100 \qquad (2)$$

$$S_i \ (\%) = (c_i/c_{CIT,converted}) \cdot 100 \qquad (3)$$

The quantification of the enantioselectivity is defined by enantiomeric excess, which is defined as the absolute difference between the mole fraction of each enantiomer [20].

$$ee_{(+)-CAL} \ (\%) = (c_{(+)-CAL}-c_{(-)-CAL})/(c_{(+)-CAL}+c_{(-)-CAL}) \cdot 100 \qquad (4)$$

RESULTS AND DISCUSSION

The role of DMP, TFA and IL was investigated by a systematic combination of each variable (Table 1). As expected, the consecutive hydrogenation of CAL using pure Pd/SiO$_2$ leads to a small CAL yield (51%). In combination with the IL the CAL selectivity increased to 97%, but racemic CAL was formed as expected. On the other hand, by using (+)-DMP and TFA as additives an ee of 19% was obtained, although the yield decreased (21%).

When the catalyst was coated with (+)-DMP and IL, a small ee of 2% was obtained, whereas when it was coated with TFA and IL no ee was achieved. The most successful step was coating the catalyst with the combination of IL, (+)-DMP and TFA. No consecutive hydrogenation of CAL was observed when CAL selectivity was kept at a

Table 1. Hydrogenation of citral using Pd/SiO$_2$ as catalyst in combination with IL, (+)-DMP and TFA[a].

#	Catalyst	X_{CIT} (%)	S_{CAL} (%)	Y_{CAL} (%)	$ee_{(+)-CAL}$ (%)
1	Pd/SiO$_2$	77	66	51	0
2	Pd/SiO$_2$/IL[b]	19	97	18	0
3	Pd/SiO$_2$ + DMP + TFA[c]	41	52	21	19
4	Pd/SiO$_2$/IL/DMP[d]	50	66	33	2
5	Pd/SiO$_2$/IL/TFA[e]	7	48	3	0
6	Pd/SiO$_2$/IL/DMP/TFA[f]	69	77	53	44

[a]Conditions: 353 K, 0.5 g Pd/SiO$_2$, 10 mL citral, 150 mL n-hexane, 20 bar, 60 min.
[b]Catalyst coated with 0.25 g IL.
[c]0.25 g (+)-DMP and 0.1 mL TFA as additive in solvent.
[d]Catalyst coated with 0.25 g IL and 0.25 g (+)-DMP.
[e]Catalyst coated with 0.25 g IL and 0.1 mL TFA.
[f]Catalyst coated with 0.25 g IL, 0.25 g (+)-DMP and 0.1 mL IL.

high level, and an ee of 44% was achieved. Besides suppressing the consecutive hydrogenation of CAL (Table 1 line 1 vs. 2), a major advantage of the IL is the fixation of (+)-DMP and TFA, both in small amounts, on the catalyst surface. In consequence, this leads to an increase in ee (Table 1 line 3 vs. 6). To examine the possibility of increasing the ee and the yield the effect of reaction temperature and pressure was investigated (Table 2).

As the results in table 2 show, the conversion of citral rises with the reaction temperature and reaches a constant level of 69% at 353 K. An ee of 9% is reached at a temperature of 313 K, whereas it increases up to 44% at 353 K. The selectivity to CAL decreases slightly with rising reaction temperature and with decreasing pressure. The conversion and the ee slightly increase with decreasing pressure reaching 78% and 47%, respectively at a pressure of 5 bar. The low reaction rate at higher pressures may be the result of a higher hydrogen surface coverage at higher pressure. But due to the complexity of the catalyst system, this context needs to be investigated in further studies. In a final step, the enantiomeric excess was significantly increased by changing the reaction solvent (Table 3).

Using dioxane as solvent the ee can be raised up to 55%, whereas using toluene the ee can be raised up to 61% with selectivities of 75%. A constant ee during the reaction is demonstrated in figure 3. Strong dependencies of the ee on the solvent were also found for the enantioselective hydrogenation of ethyl pyruvate catalysed by Pt catalysts modified with cinchonidine [21].

Compared to the results of Maeda *et al.* [5] the efficiency of the catalyst is significantly increased due to the use of a supported catalyst with an Ionic Liquid Layer (SCILL system) which contains the chiral modifier. To the best of our knowledge this conceptual approach is the first

Table 2. Effects of temperature and pressure on the hydrogenation of citral using Pd/SiO_2 as catalyst coated with IL, (+)-DMP and TFA[a].

| #	T (K)	p (bar)	X_{CIT} (%)	S_{CAL} (%)	Y_{CAL} (%)	$ee_{(+)\text{-}CAL}$ (%)
1	313	20	33	74	24	9
2	333	20	35	77	27	33
3	353	20	69	77	53	44
4	373	20	69	68	47	44
5	353	5	78	80	63	47
6	353	10	78	76	59	47
7	353	20	69	77	53	44
8	353	40	66	73	48	43

[a]Conditions: 313-373 K, 0.5 g Pd/SiO_2, 10 mL citral, 150 mL n-hexane, 5-40 bar, 60 min.

Table 3. Effects of temperature and pressure on the hydrogenation of citral using Pd/SiO_2 as catalyst coated with IL, (+)-DMP and TFA[a].
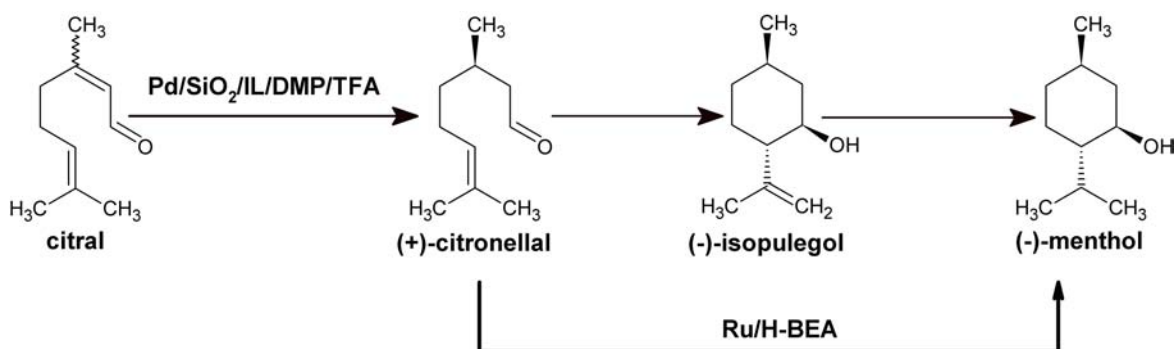
#	Solvent	X_{CIT} (%)	S_{CAL} (%)	Y_{CAL} (%)	$ee_{(+)\text{-}CAL}$ (%)
1	n-hexane	78	80	63	47
2	dioxane	71	83	59	55
3	toluene	56	75	42	61
4	toluene[b]	99	77	76	62

[a]Conditions: 353 K, 0.5 g Pd/SiO_2, 10 mL citral, 150 mL solvent, 5 bar, 60 min.
[b]after 4 h.
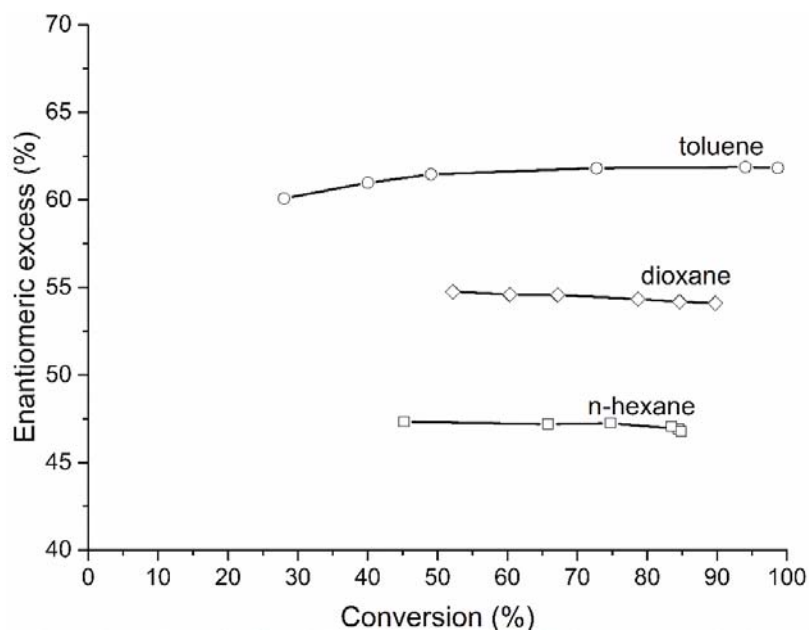
Figure 3. Enantiomeric excess of (+)-CAL vs. conversion of CIT using Pd/SiO$_2$ as catalyst coated with IL, (+)-DMP and TFA. Conditions: 353 K, 0.5 g Pd/SiO$_2$, 10 mL citral, 150 mL solvent, 20 bar.

Figure 4. Simplified reaction network of the transformation of citral to menthol. A modified SCILL catalyst is used in the first step. The combined second and third step can be realized by using bifunctional Ru/H-BEA catalysts.

example of a heterogeneously catalysed enantioselective citral hydrogenation. By using similar CIT:DMP ratios the reaction time was reduced from 21 h to 4 h (Table 3, line 4), thus increasing the space-time-yield (related to the amount of DMP) by a factor of 6.5 (1.1 vs. 6.9 g_{CAL} g_{DMP}^{-1} h^{-1}).

CONCLUSION

In the present study we showed that using a heterogeneous Pd/SiO$_2$ catalyst coated with an Ionic Liquid, (R)-(+)-2-(Diphenylmethyl)pyrrolidine and trifluoroacetic acid citral can be hydrogenated enantioselectivly and a further hydrogenation of the obtained citronellal can be avoided. At first it was demonstrated that only the combination of (R)-(+)-2-(Diphenylmethyl)pyrrolidine and trifluoroacetic acid leads to an enantiomeric excess, which can be further improved *via* fixation of the modifier and trifluoroacetic acid on the catalyst using an IL. Additionally, low pressures, a temperature of 353 K and toluene as solvent proved to be the appropriate reaction conditions for the formation of citronellal with high selectivity and high yield as well as with an enantiomeric

excess of 61% for (+)-citronellal. The obtained (+)-citronellal can be converted to (-)-menthol *via* a one-pot-citronellal-conversion using bifunctional Ru/H-BEA catalysts (Figure 4) [15, 16].

CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

REFERENCES

1.   Leffingwell, J. C. 2009, Handbook of Cosmetic Science and Technology, 3, 661-675.
2.   Lawrence, B. M. 2006, Mint: The Genus Mentha, CRC Press, New York.
3.   Schäfer, B. 2013, Chem. unserer Zeit, 47, 174-182.
4.   Maeda, H. and Hori, Y. 2010, WO 2010140636 A1.
5.   Maeda, H., Yamada, S., Itoh, H. and Hori, Y. 2012, Chem. Commun., 48, 1772-1774.
6.   Claus, P. and Önal, Y. 2008, Handbook of Heterogeneous Catalysis, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, p. 3308.
7.   Arras, J., Steffan, M., Shayeghi, Y. and Claus, P. 2008, Chem. Commun., 4058-4060.
8.   Wörz, N., Arras, J. and Claus, P. 2011, Appl. Catal. A, 391, 319-324.
9.   Arras, J., Steffan, M., Shayeghi, Y., Ruppert, D. and Claus, P. 2009, Green Chem., 11, 716-723.
10. Arras, J., Ruppert, D. and Claus, P. 2009, Appl. Catal. A, 371, 73-77.
11. Arras, J., Paki, E., Roth, C., Radnik, J., Lucas, M. and Claus, P. 2010, J. Phys. Chem. C, 114, 10520-10526.
12. Mertens, P., Verpoort, F., Parvulescu, A.-N. and De Vos, D. 2006, J. Catal., 243, 7-13.
13. Iosif, F., Coman, S., Parvulescu, V., Grange, P., Delsarte, S., De Vos, D. and Jacobs, P. 2004, Chem. Commun., 11, 1292-1293.
14. Neațu, F., Coman, S., Pârvulescu, V. I., Poncelet, G., De Vos, D. and Jacobs, P. 2009, Top. Catal., 52, 1292-1300.
15. Plößer, J., Lucas, M. and Claus, P. 2014, J. Catal., 320, 189-197.
16. Plößer, J., Dedeaga, F., Lucas, M. and Claus, P. 2016, Appl. Catal. A, 516, 100-108.
17. Wörz, N. 2014, Dissertation, TU Darmstadt.
18. Thommes, M., Kaneko, K., Neimark Alexander, V., Olivier James, P., Rodriguez-Reinoso, F., Rouquerol, J. and Sing Kenneth, S. W. 2015, Pure Appl. Chem., 87, 1051.
19. Fehrmann, R., Riisager, A. and Haumann, M. 2014, Supported Ionic Liquids: Fundamentals and Applications, Wiley.
20. Moss, G. P. 1996, Pure Appl. Chem., 68, 2193.
21. Wells, P. and Wilkinson, A. 1998, Top. Catal., 5, 39-50.