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COMMUNICATION

A dual catalyst system provides the shortest pathway for L-menthol synthesis†

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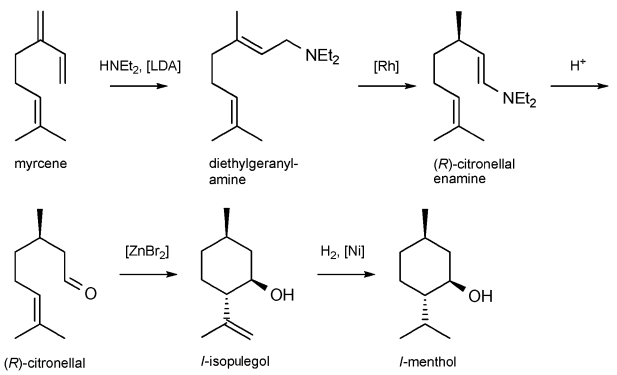
We have demonstrated that a combination of enantiopure 2-diarylmethylpyrrolidines and heterogeneous Pd/$BaSO_4$ is an efficient catalytic system for the asymmetric hydrogenation of citral, specifically, a mixture of *E*-citral and *Z*-citral in any ratio, and that citronellal is obtained with high enantioselectivity. This dual catalyst system provides a new and more economical route to L-menthol.

L-Menthol ((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol), a stereoisomer of menthol, is an important aroma chemical that occurs naturally in peppermint oil and is widely used as a cooling agent. Today, Takasago International Corporation produces more than 2×10^6 kg of L-menthol per year by employing the 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-Rh complex-catalyzed enantioselective isomerization of geranylamine to citronellal enamine as the key reaction; this reaction proceeds in 96–99% ee (Scheme 1).[1]

Recently, BASF presented a simplified 4-step synthesis method of L-menthol from citral.[2] However, rectification of *E*/*Z* mixtures to obtain high purity *Z*-citral (neral) is needed in their method (Scheme 2).



Scheme 1 Takasago L-menthol synthesis.

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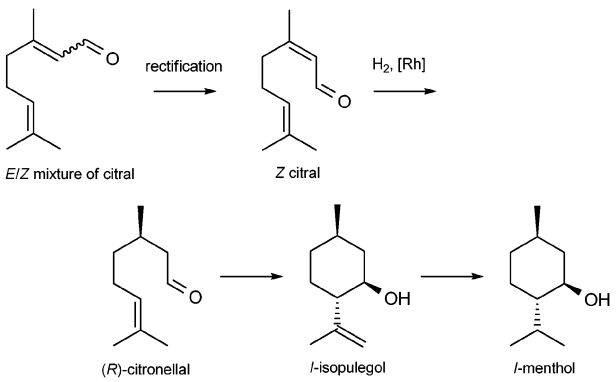
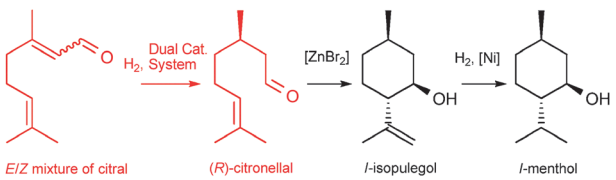
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, copies of 1H and ^{13}C-NMR spectra. See DOI: 10.1039/c2cc16548a



Scheme 2 BASF L-menthol synthesis.

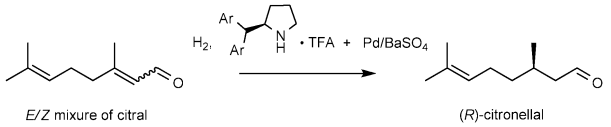
During our continuing efforts to develop more efficient synthetic routes to synthesize L-menthol, we became interested in the development of enantioselective catalysis of the hydrogenation of an *E*/*Z* mixture of citral since this provides a new and more economical route to L-menthol. However, the enantioselective hydrogenation of *E*/*Z* mixtures of prochiral olefinic substrates remains largely unsuccessful because it is essential for the substrate to have high geometrical purity for attaining high enantioselectivity (Scheme 3).[2]

However, MacMillan *et al.*,[3a,b] List *et al.*,[3c–e] and Kudo *et al.*[3f] have recently reported that the enantioselective organocatalytic hydride reduction of *E*- and *Z*-β-methylcinnamaldehyde using Hantzsch esters affords an identical enantiomer to β-phenylbutyraldehyde with excellent levels of enantioselectivity. Taking these previous works into consideration, we decided to employ hydrogen gas as the hydrogen source by performing activation using a heterogeneous Pd/$BaSO_4$ catalyst; a small amount of chiral cyclic amine was then used as an asymmetric organocatalyst for forming the iminium salts. After many attempts, we found that a dual catalyst system comprising Pd/$BaSO_4$ and chiral 2-diarylmethylpyrrolidine is effective for the asymmetric hydrogenation of citral (eqn (1)). In this communication, we describe our results and



Scheme 3 New route to L-menthol.

discuss the mechanism of the newly developed asymmetric dual catalysis.



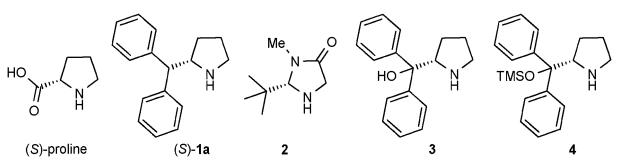
(1)

First, we conducted preliminary experiments using several chiral cyclic amines as the organocatalyst for the asymmetric hydrogenation of citral. The hydrogenations of citral (*E*-citral : *Z*-citral = 50 : 50) were carried out in the presence of 5%-Pd/$BaSO_4$[4] (0.1 mol%), chiral amines (1.6–1.9 mol%), and trifluoroacetic acid (TFA) (1.6–1.9 mol%) under atmospheric pressure of H_2 in *t*-BuOH/H_2O (92 : 8 v/v) at 50 °C; the results are summarized in Table 1. Asymmetric hydrogenations of isophorone catalyzed by heterogeneous Pd and (*S*)-proline,[5a] and by heterogeneous Pd and **3**,[5b] both without TFA, were reported. When we used (*S*)-proline as a catalyst, the hydrogenation of citral gave low conversion and low optical yield of citronellal (entries 1 and 2). We carried out hydrogenation of citral catalyzed by Pd/$BaSO_4$ and **3** without TFA as described above. Optical purity of corresponding citronellal is much lower than that of our catalyst system (entries 5 and 6).

In all cases, (*S*)-pyrrolidine catalysts yielded (*S*)-citronellal, and significantly, (*S*)-2-diphenylmethyl-pyrrolidine (**1a**) provided the highest enantioselectivity among the cyclic amines.

Encouraged by the preliminary results, we then prepared a series of chiral 2-diarylmethylpyrrolidines with different alkyl substituents on the benzene rings and examined their effectiveness as asymmetric organocatalysts. The results are shown in Table 2. Interestingly, the introduction of an alkyl group at the *para*-positions of the benzene rings in **1** led to a significantly enhanced % ee (entries 2–7). For instance, the use of 2-di(*p*-*tert*-butylphenyl)methylpyrrolidine (**1b**) afforded 84% ee and 74% chemical yield. More interestingly, the introduction of the hydroxy group at the 4-position of **1b** further improved the

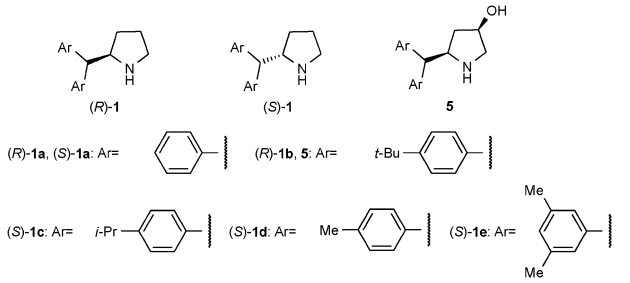
Table 1 Scope of amine catalyst for asymmetric hydrogenation of citral[a]



Entry	Amine	Conversion[b] (%)	Yield[b] (%)	% ee[c]
1[d]	(*S*)-Proline	100	37	3 (*S*)
2	(*S*)-Proline	52	38	6 (*S*)
3	(*S*)-**1a**	75	62	77 (*S*)
4	**2**	82	55	40 (*S*)
5[d]	**3**	85	35	5 (*S*)
6	**3**	52	39	69 (*S*)
7	**4**	96	72	74 (*S*)

[a] The hydrogenation of citral (*E*/*Z* = 50/50; 13.1 mmol) was conducted in the presence of 5%-Pd/$BaSO_4$ (0.1 mol%), chiral amines (1.6–1.9 mol%), and trifluoroacetic acid (TFA) (1.6–1.9 mol%) under atmospheric pressure of H_2 in *t*-BuOH/H_2O (92 : 8 v/v) (2.0 mL) at 50 °C for 21 h. [b] Determined by gas liquid chromatography (GLC) analysis. [c] Enantioexcess was determined by chiral GLC analysis. [d] Without TFA.

Table 2 Asymmetric hydrogenation of citral: substituent effect[a]

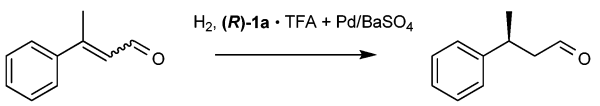


Entry	Amine	Conversion[b] (%)	Yield[b] (%)	% ee[c]
1	(*R*)-**1a**	79	65	77 (*R*)
2	(*R*)-**1b**	88	74	84 (*R*)
3[d]	(*R*)-**1b**	100	77	84 (*R*)
4[d,e]	(*R*)-**1b**	99	76	85 (*R*)
5[d,f]	(*R*)-**1b**	94	63	83 (*R*)
6	(*S*)-**1c**	92	80	84 (*S*)
7	(*S*)-**1d**	79	67	80 (*S*)
8	(*S*)-**1e**	73	57	77 (*S*)
9	**5**	84	58	89 (*R*)
10[g]	**5**	100	78	88 (*R*)

[a] Unless otherwise noted, the reactions were performed in the same manner as described in Table 1. [b] Determined by gas liquid chromatography (GLC) analysis. [c] Enantioexcess was determined by chiral GLC analysis. [d] The hydrogenation reaction was performed at 60 °C. [e] *E*-citral (*E*/*Z* = 91/9) was used as the substrate. [f] *Z*-citral (*E*/*Z* = 3/97) was used as the substrate. [g] The hydrogenation reaction was performed in the presence of **5** (1.0 mol%) and 5%-Pd/$BaSO_4$ (0.1 mol%) in *t*-BuOH/H_2O (92 : 8 v/v) (2.0 mL) at 60 °C for 21 h.

enantioselectivity up to 89% ee (entry 9). It should be emphasized that the sense and degree of enantioselectivity are essentially independent of the geometry of the substrate used (entries 3–5).

When we carried out hydrogenation of *E*- and *Z*-β-methylcinnamaldehyde, the enantioselectivity of corresponding (*S*)-3-phenylbutyraldehyde was 36%.[3b,d,6] So we need to design other suitable chiral 2-diarylmethyl-pyrrolidines for the hydrogenation (eqn (2)).

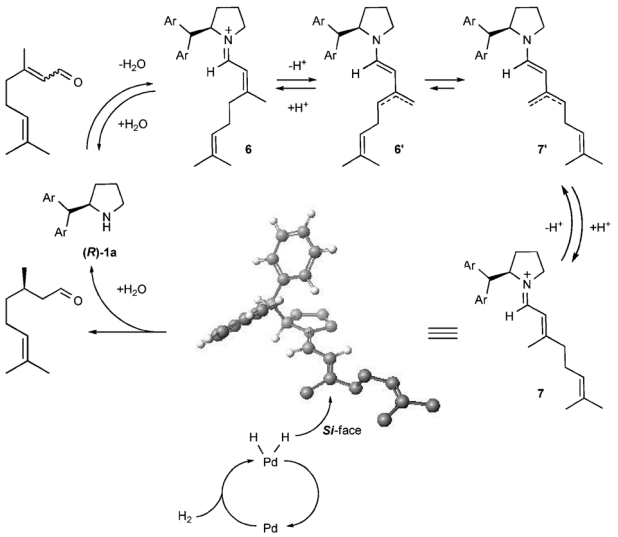


(2)

Although the high complexity of the dual catalyst system renders mechanistic analysis difficult, the mechanism is considered to be similar to that proposed for an enantioselective organocatalytic reduction process using Hantzsch esters.[3a,d] A plausible reaction mechanism is depicted in Scheme 4; here, the equilibrium between the two iminium cations (**6** and **7**) initially formed from citral and (*R*)-**1a** might be rapidly shifted to sterically more stable *E*-iminium species **7**[7] that then undergoes hydrogenation onto its olefinic bond preferentially from *Si*-face to become (*R*)-citronellal.

To the best of our knowledge, our work presents the first successful example of the enantioselective hydrogenation of an *E*/*Z* citral mixture by the cooperation of an organocatalyst and a heterogeneous palladium catalyst.

In summary, we have developed a new and efficient dual catalyst system for the asymmetric hydrogenation of citral to



Scheme 4 Plausible reaction mechanism.

afford (*R*)- or (*S*)-citronellal in high enantiopurities; the use of enantiopure 2-diarylmethylpyrrolidines as the organocatalyst was the key factor for our success. We have thus established an important basis for the heterogeneous metal-catalyzed asymmetric hydrogenation of prochiral olefins, including α,β-unsaturated aldehydes and ketones. Further researches for more effective chiral organocatalysts are in progress in our laboratory.

We thank emeritus Prof. Dr Takeshi Nakai of Tokyo Institute of Technology and Prof. Dr Masahiro Terada of Tohoku University for their helpful discussions.

Notes and references

1 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, Inc., New York, USA, 1994, pp. 95–96.

2 (*a*) *Asymmetric Catalysis on Industrial Scale*, ed. H.-U. Blaser and H.-J. Federsel, Wiley-VCH, Weinheim, Germany, 2010, pp. 187–205; (*b*) G. Heydrich *et al.*, *US 2010/0249467 A1*, 2010; (*c*) T.-P. Dang, P. Aviron-Violet, Y. Colleuille and J. Varagnat, *J. Mol. Catal.*, 1982, **16**, 51.

3 (*a*) S. G. Ouellet, A. M. Walji and D. W. C. MacMillan, *Acc. Chem. Res.*, 2007, **40**, 1327. References are cited therein; (*b*) S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 32; (*c*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660; (*d*) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108; (*e*) S. Mayer and B. List, *Angew. Chem., Int. Ed.*, 2006, **45**, 4193; (*f*) K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Tetrahedron: Asymmetry*, 2009, **20**, 461.

4 We tried to use various heterogeneous catalysts, $Pd/CaCO_3$/$Pb(OAc)_2$, Pd/C/quinoline, Pd/Al_2O_3, Pd/C, Rh/C, and Pt/Al_2O_3 *etc.* and various acids, HCl, HBr, AcOH, $ClCH_2CO_2H$ *etc.* and various solvents, MeOH, EtOH, THF, toluene *etc.* Consequently, the combination of $Pd/BaSO_4$, TFA, and *t*-BuOH/H_2O (92 : 8 v/v) showed the best results for yield and enantioselectivity of citronellal.

5 (*a*) N. Gyorffy, A. Tungler and M. Fodor, *J. Catal.*, 2010, **270**, 2; (*b*) E. Sipos, A. Tungler, I. Bitter and M. Kubinyi, *J. Mol. Catal.*, 2002, **186**, 187.

6 The hydrogenation reaction of β-methylcinnamaldehyde (*E*/*Z* = 88 : 12, 1.0 g, 6.84 mmol) was performed in the presence of (*R*)-**1a** (1.6 mol%) and 5%-Pd/C (0.17 mol%) in toluene (2.0 mL) at 25 °C for 21 h.

7 In other words, this asymmetric process involves a dynamic kinetic resolution of the *E*- and *Z*-iminium species. It is interesting to note that when the reactions using (*R*)-**1b** were performed at a lower temperature (25 °C), % ee's decreased with a decrease in the *E*-purity of the substrate (83% ee from 91%*E*, 73% ee from 50%*E*, and 56% ee from 3%*E*). This observation probably reflects the scenario in which the isomerization rate of **6–7** is not sufficiently rapid to complete the dynamic kinetic resolution.

