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# Sn-Beta zeolite as diastereoselective water-resistant heterogeneous Lewis-acid catalyst for carbon–carbon bond formation in the intramolecular carbonyl–ene reaction

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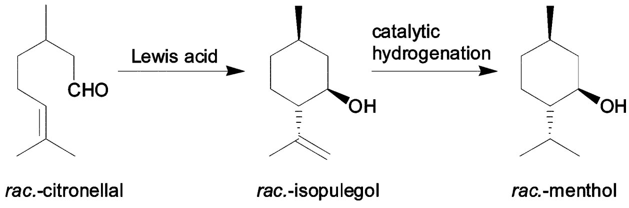
**The water-tolerant Lewis acid Sn-Beta isomerises citronellal to isopulegol with high diastereoselectivity working in batch or in fixed bed reactors with very high turnover numbers.**

(−)-Menthol is known for its refreshing diffuse odour characteristic of peppermint and strong physiological cooling effect.[1] Therefore, it has, contrary to other diastereo- or enantiomers, a commercial importance for dentifrices, cosmetics and pharmaceuticals. Synthetically it can be produced by Lewis-acid catalysed cyclisation of citronellal with subsequent catalytic hydrogenation (Scheme 1). The important feature of the cyclisation is the diastereoselectivity towards the isopulegol since the other isomers will produce commercially less interesting products. $ZnBr_2$ has been identified as the most suitable Lewis acid for this process providing a 94 : 6 diastereoselectivity towards isopulegol[2] and it is employed as promoter in the actual industrial process for the cyclisation yielding 92% of isopulegol.[3] However, the stoichiometric amounts of zinc bromide required may cause waste disposal problems since it acts as marine toxin.[4] Another critical factor is the hygroscopic character of anhydrous zinc bromide and the fact that wet zinc bromide is much less active and selective than the anhydrous form.

To overcome these drawbacks several soluble metal complexes have been tested for the cyclisation.[5] Thus, triethylaluminium and 2,6-diphenylphenol with a molar ratio of 1 : 3 has been used giving yields of 95%. Unfortunately, the catalyst is destroyed with NaOH after the reaction and cannot be recovered.[5] Scandium tris(trifluoromethylsulfonate) also works in homogeneous phase using a halogenated solvent. It gave at 25 °C a diastereoselectivity of 80 : 20 with yield of 58%, while at −78 °C the diastereoselectivity increased up to 94 : 6.[6] Other soluble catalysts have also been used for performing the selective cyclisation of citronellal, but the yields obtained were lower than with $ZnBr_2$.[5]

Finding a heterogeneous catalyst for this cyclisation that can give similar yields as $ZnBr_2$ under catalytic amounts, and could perform with high turnover numbers (TON, moles of substrate converted per mol of active sites) is a matter of much interest from the academic as well as from the industrial point of view. With this purpose zirconium-exchanged montmorillonite[7] and zinc impregnated commercial silicas[3] have been reported. In both cases the metal was employed in catalytic amounts and proceeded several cycles. Furthermore, it has been reported that the montmorillonite can be recycled without loss of activity and in five cycles, an overall TON of 100 has been achieved. With respect to the diastereoselectivity both systems reach high selectivities of 85–90%.† Other heterogeneous catalysts — based on Brønsted acid sites — were less successful since side products resulting from etherification, cracking or dehydration occur.[8]



**Scheme 1** Industrial production of menthol from Lewis-acid catalysed cyclisation of citronellal with subsequent catalytic hydrogenation.

Recently, we have introduced novel solid Lewis acids that involve tin incorporated into a Beta zeolite network (Sn-Beta)[9] or into a MCM-41 molecular sieve.[10] This type of catalysts has already been applied successfully to the Baeyer–Villiger reaction with hydrogen peroxide[11] and to the Meerwein–Ponndorf–Verley reduction.[12] We will show here that this water-tolerant Lewis acid (Sn-Beta) can be successfully applied to the carbonyl–ene reaction in the cyclisation of citronellal to isopulegol.

The catalysts have been synthesized as reported elsewhere.[11] Samples A, B and C of Sn-Beta have Si : Sn ratios of 250 (1 wt% of $SnO_2$), 123 (2 wt% of $SnO_2$) and 82 (3 wt% of $SnO_2$), respectively. Activity tests in batch mode were carried out as described in the following procedure: racemic citronellal (620 mg, 4 mmol) was dissolved in 3.0 g of solvent. A sample of the catalyst (50 mg) was added and the reaction mixture heated to 80 °C for 1 h. The catalyst was filtered out and the reaction mixture analysed by gas chromatography and the products were identified by GC-MS spectroscopy and the isopulegol diastereomer by comparison with the authentic sample.

When Sn-Beta zeolite was employed as catalyst in acetonitrile as solvent the conversion was almost completed after one hour and the desired product isopulegol was obtained with a selectivity higher than 98% and an 85 : 15 diastereoselectivity ratio (Table 1, entry 1). The influence of metal loading can be discussed from the results of conversion obtained with catalysts A, B and C after 5 minutes reaction time (Table 1, entries 1–3). It can be seen there that conversion increases with Sn content, but the increase of activity is not linear with Sn content. This is specially the case for the sample containing 3 wt% $SnO_2$, something which is not surprising since for this level of metal substitution, not all of the metal is tetrahedrally coordinated in framework positions.[11] The reaction proceeded smoothly in other polar solvents as dioxane, *tert.*-butanol or nitromethane (Table 1, entries 5–7) and the yields of the desired product were similar. The isomerisation of citronellal into isopulegol could be carried out without solvent. However, in this case the reaction stopped at a conversion level of 67% and the diastereoselectivity was slightly lower (Table 1, entry 8). It should

**Table 1** Sn-Beta catalysed cyclisation of citronellal in different solvents

| Sn-Beta | | | Conv.[a] | Select.[b] | Diastereosel.[c] |
|---|---|---|---|---|---|
| Entry | Sample | Solvent | [%] | [%] | [%] |
| 1 | A | Acetonitrile | 97 (47) | > 98 | 85 |
| 2 | B | Acetonitrile | 99 (63) | > 98 | 83 |
| 3 | C | Acetonitrile | 99 (66) | > 98 | 81 |
| 4 | B | Acetonitrile[d] | 64 | > 98 | 81 |
| 5 | C | Dioxane | 99 | > 98 | 78 |
| 6 | B | *tert*-Butanol | 99 | > 98 | 82 |
| 7 | B | Nitromethane | 99 | > 98 | 80 |
| 8 | B | — | 67 | > 98 | 72 |

[a] Conversion after 1 h and in parenthesis after 5 min. [b] Selectivity for the four diastereomeric pulegols with respect to other products. [c] Selectivity for the isopulegol diastereomer with respect to the other three diastereomers. [d] At 40 °C reaction temperature.

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be noted that water present in the substrate or the solvent does not impede the reaction and special precautions were not necessary.

When the concentration of the substrate solution was increased from 17 wt% to 29 wt% and 38 wt%, the TON increased from *ca.* 600 to 1000 and 1350, respectively. This is more than one order of magnitude better than the best-known heterogeneous catalyst.

Superiority of the tin over other Lewis acids introduced into the zeolite framework is seen in Table 2. Ti-Beta gave lower conversion (Table 2, entry 3). Additionally, the diastereoselectivity with respect to the isopulegol is much lower for the titanium-containing material with only 56% *vs.* 85% for Sn-Beta (*cf.* Table 2, entries 1 and 3). Brønsted-acidic Beta zeolite with a comparable hydrophobicity[13] as Sn-Beta in the same reaction conditions also gave only cyclisation without any side-products. However, again the diastereoselectivity towards the desired product was lower (63%; Table 2, entry 2) and the conversion was only 50% *vs.* full conversion for Sn-Beta. The origin of the activity in the Sn-Beta can be attributed to the tin since the all-silica Beta sample has no activity (Table 2, entry 4).

One attempt to improve the diastereoselectivity by lowering the reaction temperature, as it has been done successfully in other cases,[6] did not produce any improvement. Thus, when the temperature was lowered from 80 °C to 40 °C, similar selectivities were obtained but the conversion was decreased significantly (Table 1, entry 4).

We have seen that the process can also be carried out in a fixed bed continuous reactor. Thus, 500 mg of catalyst B were filled into a stainless steel reactor (inner diameter 4 mm, length 13 cm), and heated to 80 °C. A solution of citronellal in acetonitrile (50 wt%) was passed through with a rate of 5 g $h^{-1}$. From Fig. 1 it can be seen that both conversion and diastereoselectivity remain constant for at least 48 h at a 99% and 83% level, respectively. Over this period 118 g of citronellal were converted which implies that each metal site performed 11 500 reaction cycles on an average. In comparison with the heterogeneous Zn or Zr materials this represents an improvement of two orders of magnitude. No leaching of Sn was detected when working in either fixed bed or in batch reactor.

In summary, Sn-Beta has been employed for the first time in a reaction that involves carbon–carbon bond formation. The catalytic performance with respect to conversion is much superior to conventional heterogeneous catalysts used for this reaction. Moreover, this catalyst does not require the usual precautions against humidity needed for normal Lewis acids. The stability of the Sn-Beta zeolite makes this catalyst suitable for applications in a fixed bed continuous reactor. We are working at present on the improvement of the diastereoselectivity.

**Table 2** Cyclisation of citronellal in acetonitrile catalysed by different Beta zeolites

| Entry | Catalyst | Metal loading [wt%] | Conv. [%] | Select.[a] [%] | Diastereosel.[b] [%] |
|---|---|---|---|---|---|
| 1 | Sn-Beta (B) | 2.0 $SnO_2$ | 99 | > 98 | 83 |
| 2 | Al-Beta | 2.8 $Al_2O_3$ | 50 | > 98 | 63 |
| 3 | Ti-Beta | 2.0 $TiO_2$ | 35 | > 98 | 56 |
| 4 | Pure silica Beta | — | 0 | | |

[a] Selectivity for the four diastereomeric pulegols with respect to other products. [b] Selectivity for the isopulegol diastereomer with respect to the other three diastereomers.

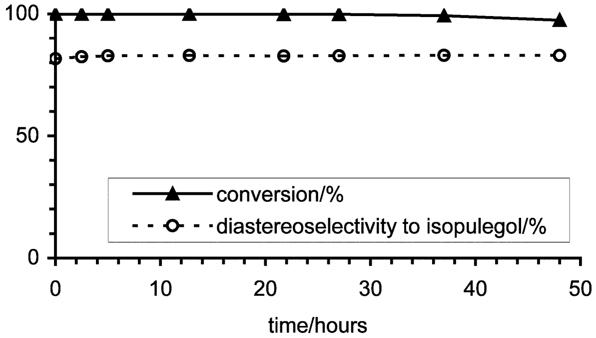

**Fig. 1** Conversion and diastereoselectivity for the cyclisation of citronellal catalysed by Sn-Beta in a fixed bed.

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## Notes and references

† As-prepared Zn-silicas (ref. 3) gave 78–86% diastereoselectivities, however, when washed bromide free the selectivity dropped to 70%. This suggested that large amounts of $ZnBr_2$ were able to modify the reaction selectivity, even though it did not influence the rate of reaction. In the $Zr^{4+}$-montmorillonite case (ref. 7), for the diastereoselectivity only two isomers, the isopulegol and the neo-isopulegol have been taken into account and a 90 : 10 ratio determined by $^1H$ NMR spectroscopy at a 91% yield.

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