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Highly Selective Aluminium-Catalysed Intramolecular Prins Reaction for L-Menthol Synthesis

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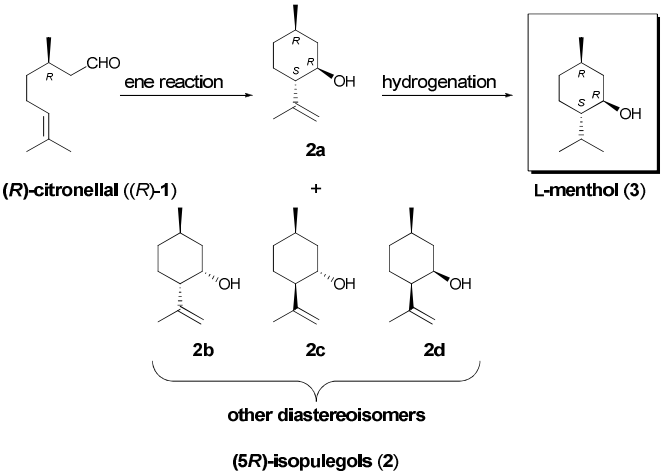
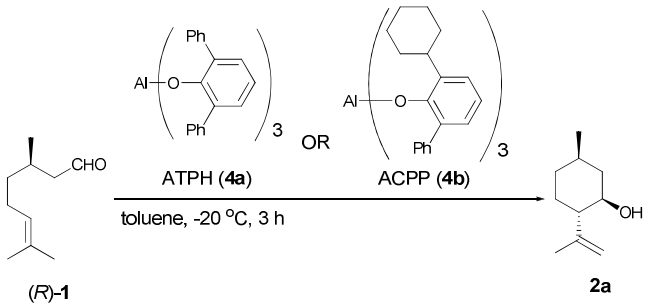
Aluminium complex bearing 2-cyclohexyl-6-phenylphenol afforded (5*R*)-*n*-isopulegol from (*R*)-citronellal via the intermolecular Prins reaction with an exceptionally high diastereoselectivity. Using this reaction, L-menthol was obtained with an excellent diastereoselectivity.

Intermolecular and intramolecular ene reactions, especially the Prins reaction between carbonyl and olefin compounds with Lewis or Brønsted acids, have received great attention.[1] A common application of the Prins reaction is the synthesis of (5*R*)-isopulegols (**2**) from (*R*)-citronellal ((*R*)-**1**) (Scheme 1).



Scheme 1. Synthesis of L-menthol (**3**) from (*R*)-citronellal (**1**).

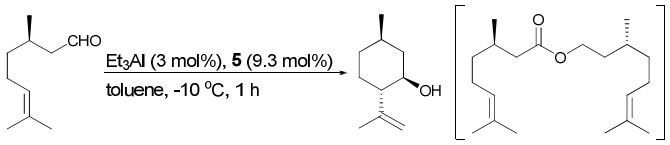
These are valuable intermediates for the synthesis of L-menthol (**3**), one of the most popular fragrances in the world;[2] notably, only (5*R*)-*n*-isopulegol (**2a**) leads to the formation of (**3**). Hence, a variety of methods has been reported for the diastereoselective cyclisation of citronellal to isopulegol.[3-10] For instance, zinc bromide is used as a catalyst for this cyclisation in an industry process, which provides **2a** with 92% of diastereomeric purity.[4a] In addition, various other aluminium complexes have been recently proposed as only catalysts that afford (5*R*)-isopulegols with a high diastereoselectivity.[11-14] For instance, tris(2,6-diphenylphenoxy)aluminium complex (ATPH, **4a**),[14] which was prepared from triethylaluminium and 2,6-diphenylphenol (**5a**), has been used to carry out the Prins reaction of citronellal with a diastereoselectivity larger than 99% and 94% at 0 °C.[11] However, **4a** shows the excellent performance in a narrow temperature range. So, it's demanded a catalyst that provides higher reactivity and same diastereoselectivity, in order to apply it to a variety of industrial processes. In this work, we present aluminium catalysts with unprecedented excellent diastereoselectivity for the citronellal cyclisation.



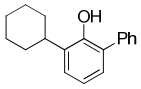
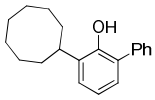
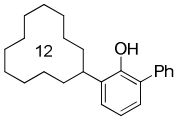
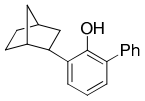
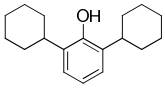
ATPH (**4a**): 54% conv., 99% selectivity of **2**, 99.2% diastereomeric purity of **2a**
ACPP (**4b**): 78% conv., 95% selectivity of **2**, 99.5% diastereomeric purity of **2a**

Scheme 2. Cyclisation of (*R*)-citronellal ((*R*)-**1**) with aluminium complexes determined by gas chromatography (GC) analysis.

Table 1. The effect of the ligand of the aluminium complexes studied on the Prins reaction



(*R*)-**1** **2a** **6**

Entry	Ligand	Conv. (%)[a]	Selectivity towards **2** (%)[a][b]	Diastereomeric purity of **2a** (%) [a]
1	 **5b**	>99	96	99.6
2[c]		98	81+8(**5**)	99.5
3[d]		63	44+43(**5**)	97.2
4[d][e]		***>99***	***98***	***99.7***
5[c][f]		>99	95	99.3
6	 **5c**	98	93	99.5
7	 **5d**	99	95	98.9
8	 **5e**	>99	98	99.4
9	 **5f**	3	80	80.4
10 [f]	 **5g**	97	22+66(**5**)	90.9

[a] Determined by gas chromatography (GC) analysis. [b] Calculated from conversion and GC area of (5*R*)-isopulegols (**2**) [c] Reacted at 0–5 °C. [d] Et_3Al (2 mol%) and **5b** (6.2 mol%) were used and reacted for 4 h. [e] Ethyl glyoxylate (8.4 mol%) were used. [f] Et_3Al (5 mol%) and ligand (15.5 mol%) were used.

Firstly, we prepared tris(2-cyclohexyl-6-phenylphenoxy) aluminium complex (ACPP, **4b**) with triethylaluminium and 2-cyclohexyl-6-phenylphenol (**5b**). (*R*)-Citronellal ((*R*)-**1**) gave (5*R*)-*n*-isopulegol (**2a**) in the presence of ACPP with 78% conversion, 95% selectivity of (5*R*)-isopulegols (**2**) and diastereoselectivity larger than 99% at -20 °C while ATPH (**4a**) afforded **2a** with 54% conversion (Scheme 2). A catalyst with such an excellent selectivity and reactivity has never been reported.

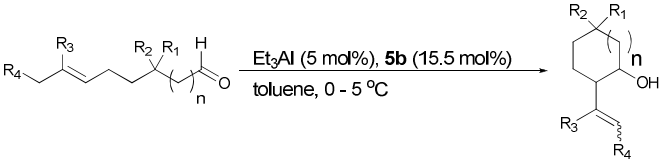
We next investigated the reactivity of ACPP with a variety of reaction conditions. In particular, 3 mol% of ACPP afforded isopulegols (**2**) with a conversion efficiency larger than 99%, selectivity of 96%, and a diastereomeric purity for **2a** of 99.6% at -10 °C (Table 1, entry 1). The dimmer ester product **6**, synthesised via the Tishchenko reaction, was obtained in 8% selectivity between 0 and 5 °C (entry 2).[15,16] 2 mol% of ACPP decreased the selectivity of **2** to 44% (entry 3). In contrast, the selectivity of **2** increased to 98% when 8.2 mol% of ethylglyoxylate was added (entry 4). ACPP afforded the cyclisation of **2** below 5 °C with a selectivity of 97%, when 5 mol% of the catalyst was used (entry 5).

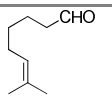
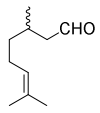
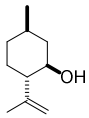
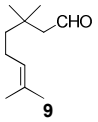
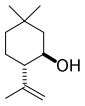
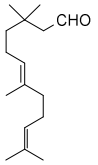
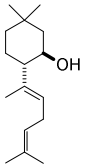
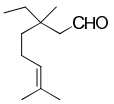
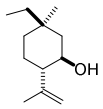
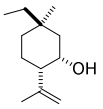
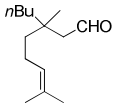
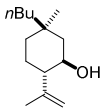
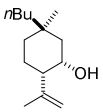
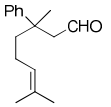
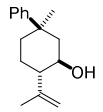
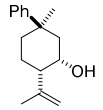
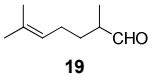
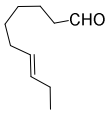
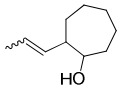
Other catalysts with cycloalkylphenylphenols (**5c, 5d**, and **5e**) afforded **2a** with good conversion, selectivity of **2** and excellent diastereomeric purity of **2a**. In particular, the catalyst (**4b**) provided **2a** with the best selectivity of **2** and diastereoselectivity (entry 1 vs entries 6-8). Interestingly, the aluminium complex bearing 2,6-dicyclohexylphenol (**5f**) not only provided **2**, but also dimmer **6** (entry 9). The 2-phenylphenol (**5g**) ligand afforded 22% selectivity of **2** and 66% selectivity of **6** (entry 10).

A variety of aldehydes ((±)-**1**, **7**, **9**, **11**, **13**, **15**, and **17**),[17-20] expected to lead to the formation of 6-membered rings, afforded the corresponding cyclisation products in the presence of the ACPP (Table 2). Interestingly, our data showed that the diastereoselectivity of citronellal analogues depends on the substituents at the 3-position of citronellal. 7-methyl-6-octenal (**7**), a citronellal structure without the 3-methyl group, was found to be less reactive, despite the 20 mol% of catalyst loading (entry 1). Racemic citronellal ((±)-**1**) gave *n*-isopulegol ((±)-**2a**) with high yield and excellent diastereomeric purity as well as (*R*)-**1** (entry 2). Citronellal analogues that bear a methyl substituent (**9** and **11**) were produced with excellent diastereoselectivity and a yield as high as 94% (entries 3 and 4). When the substituents on citronellal were larger than a methyl group (**13**, **15**, and **17**), ACPP provided the corresponding products (**14**, **16**, and **18**) with lower diastereoselectivity (entries 5–7). 3,5-Dimethylheptenal (**19**) was expected to form the 5-membered ring product (**20**); however, only trace amounts of **20** were detected in the reaction mixture using gas chromatography-mass spectrometry (GC-MS) (entry 8). *trans*-7-Decenal (**21**),[21] expected to form the 7-membered ring product (**22**), only gave trace amounts of this product according to the GC-MS data (entry 9). In order to investigate the reactivity of other carbonyl compounds, we also attempted the cyclisation of methyl citronellyl ketone[22,23] and citronellic acid methyl ester.[24] These substrates gave no product.

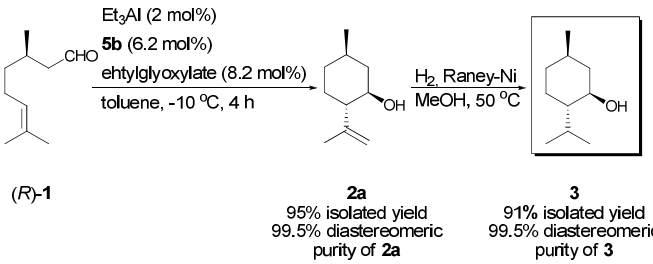
Finally, we employed ACPP for the synthesis of L-menthol (Scheme 3). Cyclisation of (*R*)-**1** with ACPP afforded **2a** (95% yield) in a 100-g scale reaction. The diastereomeric purity of **2a** reached 99.5%. Furthermore, **2a** was hydrogenated with Raney-Ni, and L-menthol (**3**) was obtained in 91% yield. The diastereomeric purity of **3** did not change upon hydrogenation.

Table 2. The Prins reaction of a variety of substrates with ACPP (**4b**)



Entry	Time (h)	Substrate	Product	Yield (%)	Diastereoselectivity ratio[a]
1[b]	19	 **7**	 **8** (*trans*)  (*cis*)	29[a]	*trans*/*cis* =81/19
2	1	 (±)-**1**	 (±)-**2a**	92	(±)-2a/(±)-**2b**, **2c**, **2d** =98.9/1.1
3	4	 **9**	 **10**	89	*trans*/*cis* =>99/<1
4[b]	19	 **11**	 **12**	94	*trans*/*cis* =>99/<1
5	4	 **13**	 **14** (1α,2β,5α)  (1α,2α,5β)	85[a]	α,2β,5α /1α,2α,5β =78/22
6	4	 **15**	 **16** (1α,2β,5α)  (1α,2α,5β)	90	1α,2β,5α /1α,2α,5β =87/13
7[c]	4	 **17**	 **18** (1α,2β,5α)  (1α,2α,5β)	74	1α,2β,5α /1α,2α,5β =62/38
8	19	 **19**	 **20**	trace	
9	19	 **21**	 **22**	trace	

[a] Determined by gas chromatography (GC) analysis. [b] Et_3Al (20 mol%) and **5b** (62 mol%) were used. [c] Et_3Al (10 mol%) and **5b** (31 mol%) were used.



Scheme 3. Synthesis of L-menthol (**3**) via the cyclisation of (*R*)-citronellal ((*R*)-**1**).

Conclusions

In summary, we present in this work an aluminium catalyst, bearing 2-cycloalkyl-6-phenylphenols, for an intramolecular Prins reaction that shows unprecedented selectivity. ACPP performs efficiently at -10 °C and affords **2a** with a diastereoselectivity as high as 99.7%. Results presented in this work indicate that ACPP may be used for the cyclisation of a variety of aldehydes, with an improved reactivity and selectivity for citronellal cyclisation compared to that obtained with ATPH.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/c000000x/

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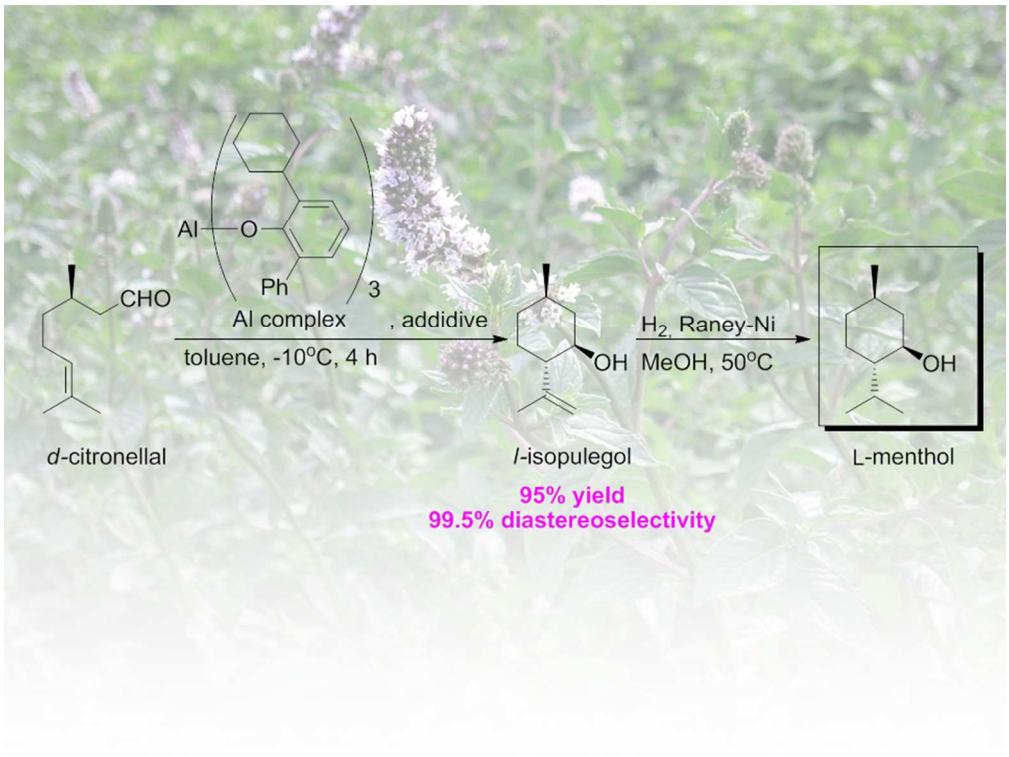

The Perfect Production of L-Menthol