Continuous catalytic "one-pot" multi-step synthesis of 2-ethylhexanal from crotonaldehyde†

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2-Ethylhexanal is synthesized directly from crotonaldehyde over a bifunctional acidic resin-supported palladium catalyst *via* hydrogenation and aldol condensation in supercritical CO_2.

The C_8 compounds obtained through the aldol condensation of butyraldehyde are industrially important and are produced worldwide on a large scale.[1] 2-Ethylhexanal, for instance, is used in disinfectants and insecticides and is employed as a synthetic intermediate for the manufacture of various organic compounds such as perfumes, paints, warning agents and leak detectors. 2-Ethylhexanol, 2-ethylhexylamines and 2-ethylhexanoic acid, which also belong to the class of industrially important C_8 chemicals, can be manufactured from this aldehyde by catalytic hydrogenation, amination and oxidation, respectively.[1]

An overview of the industrial synthetic routes to the C_8 chemicals is shown in Scheme 1. These chemicals are typically manufactured in several steps, including the hydroformylation of propylene **1** (step 1), base-catalyzed aldol condensation of butyraldehyde **2** (step 2) and subsequent gas-phase hydrogenation of 2-ethylhexenal **3** (step 3).[1] The major problem of the conventional process is that high capital cost plants are required for product purification, recovery and waste treatment, particularly in the aldol condensation step where homogeneous strong base catalysts must be handled safely.[2] Another drawback is the high reaction temperature required for the gas-phase hydrogenation. To circumvent these problems, several groups have developed alternative "one-pot" pathways to the C_8 chemicals using **1** or **2** as starting compound. Shell and Exxon developed the "Aldox process" to produce 2-ethylhexanol from **1** in one step using co-catalysts in addition to the original "oxo" catalysts.[1] However,

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the process has several inherent disadvantages:[3b] (i) a large excess amount of CO is required, (ii) the liquid space velocity in the hydroformylation is relatively low, and (iii) the selectivity to 2-ethylhexanol is rather low. Recently, Kelly and coworkers developed $Pd/Na/SiO_2$ as a solid base hydrogenation catalyst for the one-step synthesis of 2-ethylhexanal **4** from **2**,[3] while Sharma *et al.* reported $HRhCO(PPh_3)_3$ supported on hydrotalcite as a novel Aldox catalyst.[4] However, with these catalytic systems, the reactions have to be performed at relatively high temperatures (350 °C in the former and 200–250 °C in the latter case) owing to the low reaction rates and the yields of the C_8 products are moderate to low. In addition, several byproducts are formed in both cases, which renders the product purification troublesome. Moreover, the $Pd/Na/SiO_2$ catalyst is easily deactivated by poisoning caused by the product **4**.

We herein report our finding that 2-ethylhexanal **4** can be synthesized from crotonaldehyde **7** in a one-step continuous procedure with high conversion and selectivity by using a palladium-doped acidic resin catalyst§ and supercritical CO_2 ($scCO_2$) as a reaction medium.¶ The only byproduct is butyraldehyde **2**, which is also an industrially important chemical and easily separated from **4** by distillation due to the large difference in their boiling points. This new protocol is based on the efficient palladium–acid bifunctional catalysis[5] and the great miscibity of gaseous hydrogen as well as organic compounds in $scCO_2$.[6,7]

Transition-metal supported on an acidic resin of Amberlyst® 15 was first introduced by Laufer and Hoelderich in their research on the hydroxylation of benzene.[5] They loaded not only palladium but also platinum on the resin and observed an acceleration effect by the acid sites (sulfonic acid groups). Our initial study on the hydrogenation of cyclohexene to cyclohexane in $scCO_2$ revealed that 1% Pd on Amberlyst® 15 is most active for the hydrogenation of a C=C bond; 0.5% Pd, 2% Pd, a mixture of Pd (0.5%) and Pt (0.5%), 1% Ru or 1% Rh on the same resin showed much lower activity.[8] Thus we first attempted the one-step production of **4**
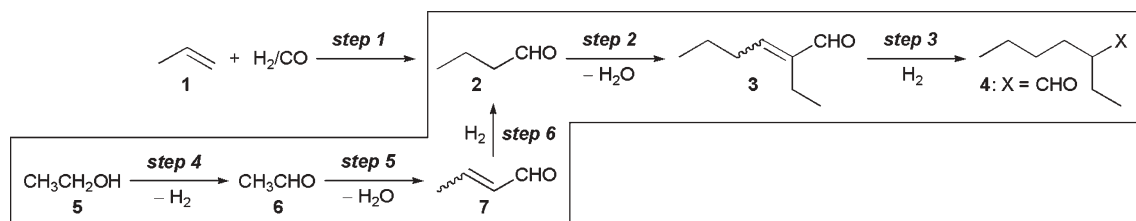
Scheme 1 Overview of the industrial synthetic routes to 2-ethylhexanal (**4**) and 2-ethylhexanol (X = CH_2OH). Reaction type: step 1, hydroformylation; step 2, aldol condensation; step 3, hydrogenation; step 4, dehydrogenation; step 5, aldol condensation; step 6, hydrogenation.

Table 1 Production of 2-ethylhexanal **4** from crotonaldehyde **7**[a]

Entry	Catalyst	Conv.[b] (%)	Select. to **4**[b] (%)	Select. to **2**[b] (%)
1	1% Pd/C[c]	94	1	55
2	1% Pd/Amberlyst-15	89	47	46
3[d]	1% Pd/Amberlyst-15	94	59	36
4[e]	1% Pd/Amberlyst-15	98	67	32
5[f]	1% Pd/Amberlyst-15	13	∼0	39

[a] Catalyst, 1.00 g; total pressure, 16 MPa; reactor temperature, 60 °C; flow rate of fluid, 1 L min^{-1}; flow rate of **7**, 0.3 mL min^{-1}; **7** : H$_2$ = 1 : 2.0. [b] Determined by GC. [c] Engelhard, 5109; particle size, *ca.* 0.5–1.4 mm. [d] **7** : H$_2$ = 1 : 3.0. [e] **7** : H$_2$ = 1 : 4.0. [f] Total pressure, 4 MPa; **7** : H$_2$ = 1 : 4.0.

from **2** by using the 1% Pd on Amberlyst® 15 catalyst (denoted 1% Pd/Amberlyst-15).[9] However, GC analysis of the product samples showed the formation of many unidentified products in considerable amounts in addition to **4**. We therefore abandoned this system.

We next used crotonaldehyde **7** as starting compound. Intriguingly, this α,β-unsaturated aldehyde was selectively converted to 2-ethylhexanal **4** and butyraldehyde **2** over 1% Pd/Amberlyst-15 in scCO$_2$ (Table 1, entries 2–4),[10] whereas 1% Pd/C with no acidity did not afford **4** (entry 1). The product samples contained a small amount of 2-ethylhexenal **3** besides **4** and **2** when feeding a lower amount of H$_2$. However, the amount of **3** was almost negligible (∼0% selectivity) at a **7** : H$_2$ molar ratio of 1 : 4.0 and the **4** + **2** selectivity achieved was almost 100% (entry 4). Increasing the amount of H$_2$ in the feed also led to an increase of conversion and selectivity to the target product **4**. Note that 1% Pd/Amberlyst-15 gave 1-butanol in a quite low selectivity of 1% and did not afford 2-ethylhexanol under the conditions of entries 2–4, while 1% Pd/C afforded 1-butanol in a higher selectivity of 9%, indicating that 1% Pd/Amberlyst-15 is a selective catalyst for C=C hydrogenations. Thus, the surface palladium species and sulfonic acid groups functioned alternately to produce **4** through a complex but clean one-step process involving hydrogenation, aldol reaction and dehydration, suppressing the formation of 1-butanol and 2-ethylhexanol (Scheme 1).

Decreasing the total pressure from 16 to 4 MPa by lowering the CO$_2$ pressure led to a drastic decrease in conversion and selectivity (entry 4 *vs.* 5). The low conversion of **7** and the much lower selectivity of **4** compared to that of **3** (24%) at 4 MPa clearly demonstrated that the hydrogenation steps were retarded at the low total pressure due to the increased mass transport limitation of gaseous hydrogen. Choosing a proper CO$_2$-pressure is thus crucial for optimizing the performance of this bifunctional catalytic system.

We finally examined the lifetime of the 1% Pd/Amberlyst-15 catalyst for the reaction of **7**. As is evident from Fig. 1, this catalyst exhibited good long-term behaviour under the conditions applied, continuing to convert **7** into **4** and **2** with quantitative conversion and ∼100% selectivity to **4** + **2** for at least 12 h. The selectivities to **4** and **2** did not significantly change throughout time-on-stream. However, the selectivity to **4** gradually decreased after 7 h accompanied by an increase in the selectivity to **2**. This might be caused by the decrease in acid sites, namely sulfonic acid groups on the resin, through the thermal decomposition by the reaction heat.[11] On the other hand, the palladium clusters were firmly fixed
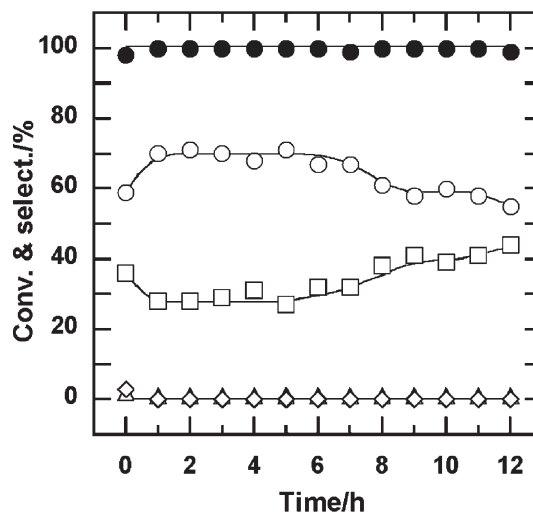

Fig. 1 Variation of the conversion and selectivity with time-on-stream over 1% Pd/Amberlyst-15. The time started from the first sampling. Catalyst, 1.00 g; total pressure, 16 MPa; reactor temperature, 60 °C; flow rate of fluid, 1 L min^{-1}; flow rate of **7**, 0.3 mL min^{-1}; **7** : H$_2$ = 1 : 4.0. Conversion, ●; selectivity to **4**, ○; selectivity to **2**, □; selectivity to **3**, ◇; selectivity to 1-butanol, △.

on the resin and stayed active throughout the longterm continuous-flowing.[12]

In conclusion, we have developed a novel palladium–acid bifunctional catalytic system composed of an easily available catalyst and scCO$_2$. The catalyst exhibits high activity, selectivity and long lifetime and affords an efficient and selective route to the industrially important 2-ethylhexanal from crotonaldehyde. The catalytic system provides the following advantageous features: (i) the only byproduct is butyraldehyde, which is also industrially important and can be easily separated by distillation, (ii) *a small excess of hydrogen is sufficient* to promote the hydrogenations owing to the great miscibility of hydrogen and **7** in scCO$_2$, (iii) the hydrogenations proceed very fast and *can be performed at low temperature (60 °C)*, (iv) under appropriate conditions the catalyst exhibits a good long-term behaviour and *seems to resist deactivation caused by the adsorption of reactant, products, CO$_2$ and byproducts (e.g., water, oligomers)* and (v) *crotonaldehyde containing stabilizers can be directly used without further purification* due to the catalyst's tolerance towards them. The present method thus may provide a promising alternative for the industrial production of the two important aldehydes.

Notes and references

§ The 1% Pd/Amberlyst-15 catalyst was prepared as follows: Into a 50-mL flask containing a stirring bar were added [Pd(NH$_3$)$_4$]Cl$_2$ (ABCR, 99%; 0.0466 g, 0.190 mmol) and deionized water (20.0 g). After stirring the mixture for homogenization, Amberlyst® 15 (Fluka, 20–50 mesh, dry (moisture ∼5%); 2.00 g) was added, and the resultant heterogeneous mixture was stirred at 80 °C for 24 h. The solid material was separated by filtration, washed with deionized water (15 mL) and dried at 100–110 °C overnight. The as-synthesized catalyst (the reference 1% Pd/C catalyst also)

was pre-reduced at 100 °C for 1 h under an H_2/N_2 flow just before its use for a reaction.

¶ **SAFETY NOTE**: *Operators handling high-pressure equipment for reactions in scCO$_2$ should take proper precautions to minimize the risk of personal injury*. The continuous-flow reactor was composed of a CO_2-compressing unit (NWA, model PM-101), a 6-port valve for introducing H_2 (Rheodyne, model 7000), an HPLC pump for feeding liquid substrates (Gilson, model 305), a tubular reactor (ETH-workshop, 35 mL volume and 13 mm diameter), an expansion unit (NWA, model PE-103), a sampling unit and a flowmeter.[13] The product sample was collected in a vial containing a known amount of toluene (internal standard substance). The mixture was then diluted with ethyl acetate and subjected to analysis by GC on an instrument equipped with FID (Hewlett Packard, model HP 6890) that had an HP-5 column (J&W Scientific, 30 m × 0.32 mm × 0.25 μm). The column temperature was as follows: 50 °C (10 min) → 20 °C min^{-1} → 250 °C (5 min). The products were identified by GC-MS and NMR.

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8 The reaction conditions were as follows. Total pressure, 16 MPa; reactor temperature, 60 °C; flow rate of fluid, 1 L min^{-1}; flow rate of cyclohexene, 0.5 mL min^{-1}; cyclohexene : H_2 = 1 : 1.8. The detailed results will be published elsewhere.

9 The reaction of **2** was performed at a total pressure of 16 MPa and a reactor temperature of 60 °C, employing a **2** : H_2 molar ratio of 1 : 2.0, where the feeding rate of **2** was 0.3 mL min^{-1}.

10 We obtained **7** ($\geqslant$99.5%, *cis* : *trans* = ~1 : 20) from Fluka and used it without further purification. Although the product contained 2,6-di-*tert*-butyl-*p*-cresol and H_2O as stabilizers, they had no poisonous effect on the catalyst.

11 The temperature of the catalyst increased to 95–120 °C during the reaction. This temperature range is below the maximum temperature recommended for the use of Amberlyst® 15 by Fluka (120 °C). However, the modification with palladium and, particularly, the high-pressure condition may promote the thermal decomposition even below 120 °C. For the same discussion, see: R. Amandi, P. Licence, S. K. Ross, O. Aaltonen and M. Poliakoff, *Org. Process Res. Dev.*, 2005, **9**, 451.

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