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New chiral modifiers in enantioselective heterogeneous catalytic hydrogenation of ethyl pyruvate over Pt/Al_2O_3: chiral amino alcohols derived from piperidine

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Abstract—New chiral and enantiopure *erythro* and *threo* 1,2-amino-alcohols **4a** and **4b** have been shown to accelerate the heterogeneous catalytic hydrogenation of ethyl pyruvate as much as cinchonidine does (with 77–100% conversion within 2 h). A diastereo dependence of the enantioselectivity is clearly observed between the *erythro* and *threo* isomers. Moreover enantiomeric ratios up to 86/14 have been obtained under classical and not optimized conditions with the *erythro*-isomer of the naphthyl compound **4a** making this compound very promising.

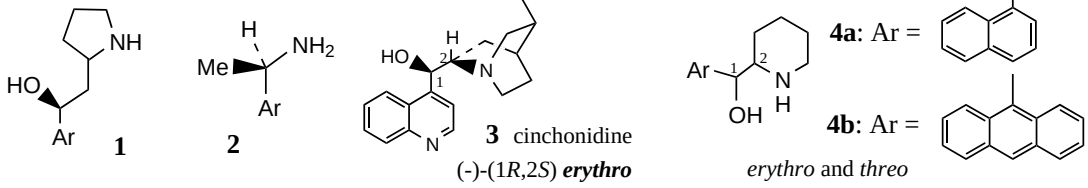
Various chiral amino-alcohols **1**[1] and aryl amines **2**[2a,b] have been designed, synthesized and tested towards the asymmetric heterogeneous hydrogenation of α-ketoesters over supported platinum catalysts but cinchonidine (CD) **3**[3] has proved so far to be the best chirality inducer. Therefore, type **4** amino alcohols having a structure closer to that of CD with the same two vicinal asymmetric carbons (C1–C2) have been synthesized, resolved and the *erythro*/*threo* structures assigned.[4]

We present here our first results concerning the use of (+)-*erythro*-**4a**, (+)-*threo*-**4a** and (+)-*threo*-**4b** for the heterogeneous hydrogenation of ethyl pyruvate into ethyl lactate over Pt/Al_2O_3 catalysts (Scheme 1).

The enantiomeric excesses of the ethyl lactate produced were determined, after distillation, by gas chromatography on a Cyclodex-B capillary column (30 m) using a HP 5890 GC-FID instrument, the e.r. values were reproducible within 1% (for the same sample). To test the amino-alcohols, we have chosen two well defined catalysts: 5% Pt/Al_2O_3 5R94 from Johnson Matthey (JMC) and 5% Pt/Al_2O_3 4759 from Engelhard (E4759). Both catalysts have been reduced at 350°C under H_2 flow for 2 h and kept under argon *prior* to utilization. AcOH was used as solvent, the reactions were run at room temperature for 2 h, stirring rate was ~500 rpm and the pyruvate, purchased from Aldrich, was distilled before use.

The results are gathered in Table 1.

The most important features of these hydrogenations are: (i) the high enantioselectivities obtained with *erythro*-**4a** over the E4759 catalyst (e.r. = 85.5/14.5–86/14; Table 1, lines 6 and 7); and (ii) the diastereoselective differentiation observed: *threo*-**4a** leading to lower e.r.



Keywords: amino-alcohols; asymmetric hydrogenation; heterogeneous hydrogenation; chiral modifier; diastereoselectivity.
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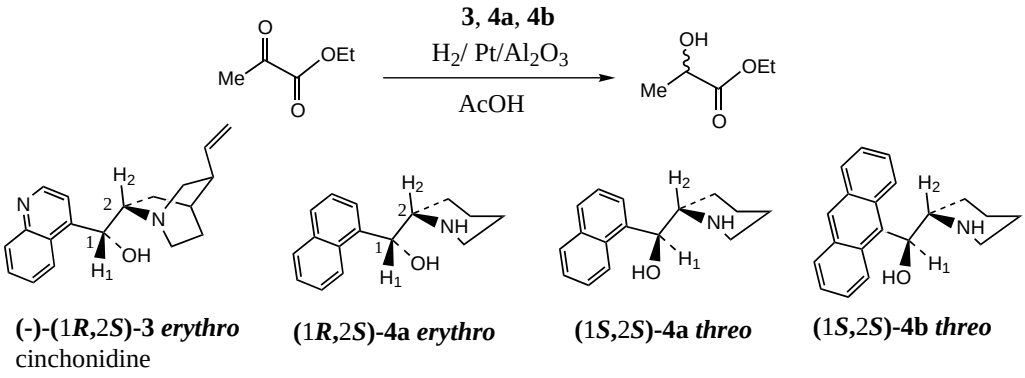

Scheme 1.

(67.5/32.5–70.5/29.5) than *erythro*-**4a** (85.5/14.5–86/14) (Table 1, compare lines 8–11 and 5–7). The same trend, but to a much larger extent, has been observed with Cinchona alkaloids.[5]

It is worth noting that the *threo*-isomers, *threo*-**4a** and *threo*-**4b**, led to similar enantioselectivities (64.5/35.5–70.5/29.5 versus 68/32–73.5/26.5) (Table 1, compare lines 12–14 and lines 8–11) and one could expect *erythro*-**4b** to provide enantioselectivities comparable to those of *erythro*-**4a**.

The absolute configurations of *erythro*-(+)-**4a**, *threo*-(+)-**4a** and *threo*-(+)-**4b** are under study by the CD-tweezer method[6] but, considering the stereo outcome known for pyruvate hydrogenations run with (1*R*,2*S*)-cinchonidine and/or (1*S*,2*R*)-cinchonine one could postulate that the *erythro*-(+)-**4a** leading to (*S*)-ethyl lactate should have the (1*S*,2*R*) configuration.[7]

The [CD]/[catal.] = 1 ratio used through all the hydrogenation experiments having been optimized for CD[7b,8] but not for the new chiral modifiers **4a**, it could well be that better e.r. will be obtained with **4a** as chiral modifier after optimization of this parameter.

It also appeared that the E4759 catalyst is more active than the JMC catalyst leading (under 10 bar) to 100% conversion instead of 54% with *erythro*-cinchonidine and (under 40 bar) to 100% conversion instead of 77% with *threo*-(+)-**4b** while they have comparable activities with *threo*-**4a**, (77 and 67% conversion, under 40 bar), with the JMC catalyst having a tendency to be slightly better (Table 1).

The new modifier, *erythro*-**4a**, is thus very promising and optimization of its structure through *N*-alkylation is under work.

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Table 1. Heterogeneous hydrogenation of ethyl pyruvate

Modifier	Catalyst	Pressure (bar)	Conversion (%)	e.r. (%)	Ee (%)[a]
Cinchonidine *erythro*-(−)-(1*R*,2*S*)-**3**	JMC	10	54	79.5/20.5	59 (*R*)
	JMC	40	100	93/7	86 (*R*)
	E4759	10	100	92.5/7.5	85 (*R*)
	E4759	40	100	89.5/10.5	79 (*R*)
erythro-(+)-**4a**	JMC	40	100	83.5/16.5	67 (*S*)
	E4759	**10**	**100**	**85.5/14.5**	**71 (*S*)**
	E4759	**40**	**100**	**86/14**	**72 (*S*)**
threo-(+)-**4a**	JMC	10	69	64.5/35.5	29 (*R*)
	JMC	40	77	68/32	36 (*R*)
	E4759	10	62	70.5/29.5	41 (*R*)
	E4759	40	67	67.5/32.5	35 (*R*)
threo-(+)-**4b**	JMC	40	77	68/32	36 (*R*)
	E4759	10	62	70.5/29.5	41 (*R*)
	E4759	40	100	73.5/26.5	47 (*R*)

[a] Absolute configuration of the *major* lactate isomer obtained.

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7. It is well known that (−)-(1*R*,2*S*)-cinchonidine and (+)-(1*S*,2*R*)-cinchonine lead respectively to (*R*)-lactate and (*S*)-lactate. See: (a) Augustine, R. L.; Tanielyan, S. K.; Doyle, L. K. *Tetrahedron: Asymmetry* **1993**, *4*, 1827; (b) Baiker, A. *J. Mol. Catal. A: Chem*. **1997**, *115*, 473; (c) Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc*. **2000**, *122*, 12675.
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