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The asymmetric hydrogenation of 2-phenethylacrylic acid as the key step for the enantioselective synthesis of Citralis Nitrile®

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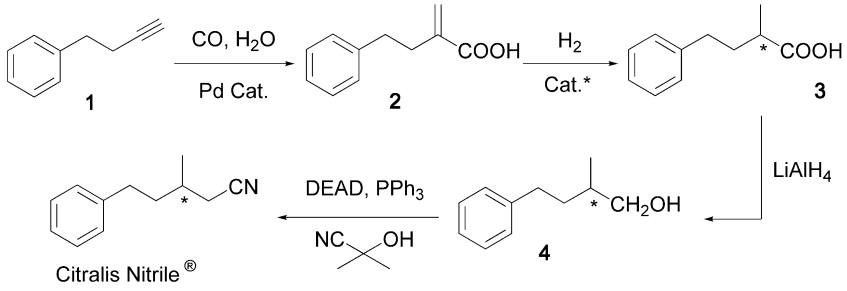
Abstract—A catalytic approach to the enantioselective synthesis of Citralis Nitrile® (3-methyl-5-phenyl-pentanenitrile, a citrus-type odorant) is described. The key step is the transition-metal catalyzed asymmetric hydrogenation of 2-phenethylacrylic acid. Among the different catalysts tested, the most efficient appears to be the one formed by combining in situ $[Ru(benzene)Cl_2]_2$ with the atropisomeric diphosphine MeOBIPHEP and triethylamine, which allows us to obtain enantiomeric excesses up to 98% under mild conditions. Very good results (ees >80%) have also been obtained using iridium cationic complexes in combination with a phosphinooxazoline ligand.

Citralis Nitrile® (3-methyl-5-phenyl-pentanenitrile) (Scheme 1) is a citrus-type odorant marketed as racemate by Aroma and Fine Chemicals (AFC).[1]

Even if today many synthetic fragrances are traded as racemates, it often occurs that the opposite enantiomers of a fragrance may induce quite different sensorial reactions, that is, have a different scent.[2] Accordingly, there is practical interest in developing preparative routes which selectively lead to the single stereomers of a fragrance.[3,4] In fact, if the two enantiomers have different olfactory activity, the use of the enantiomerically pure or of an enantiomerically enriched fragrance will provide unique odour properties, different from those of the racemate; further motivation in the use of enantiomerically enriched fragrances arises from economical and environmental concerns.

Spurred by our interest in developing practical synthetic routes to enantiomerically enriched fragrances,[5,6] we wish to report here a catalytic process (Scheme 1) for the enantioselective synthesis of Citralis Nitrile®. In this connection, it is worth mentioning that the enantiomers of Citralis Nitrile® were prepared with ee up to 70% by Pfaltz through a cobalt catalyzed asymmetric reduction of (*E*)- or (*Z*)-3-methyl-5-phenyl-pent-2-enenitrile with $NaBH_4$.[7]

Carbonylation of but-3-ynyl-benzene **1** (Aldrich) in the presence of the $Pd(OAc)_2$/2-pyridyldiphenylphosphine/



Scheme 1. Asymmetric synthesis of Citralis Nitrile®.

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methanesulfonic acid catalytic system[8,9] gives phenethylacrylic acid **2** in a 92% yield.[10] Asymmetric hydrogenation of **2** in the presence of a chiral transition-metal catalyst leads to enantiomerically enriched acid **3**. Then, the reduction of **3** to the corresponding alcohol **4** followed by a Mitsunobu type reaction[11] affords Citralis Nitrile®.

The above synthesis of acrylic acid **2** is particularly convenient because it does not only afford the olefin in a high yield, but also with a complete regioselectivity. This is of paramount importance because it is known that the metal catalyzed asymmetric hydrogen addition on isomeric olefins often gives opposite enantiomers.[6,12]

The most challenging step is the asymmetric hydrogenation of acrylic acid **2**. As a matter of fact, inspection of the literature reveals that while the asymmetric hydrogenation of α-arylacrylic acids and of disubstituted or trisubstituted acrylic acids has received much attention,[13–17] there are few studies dealing with the hydrogenation of acrylic acids bearing as the only substituent an aliphatic chain in α position, such as **2**.[18,19]

The asymmetric hydrogenation of olefin **2** was first carried out in the presence of an iridium-based catalyst (**Ir-PHOX**, Fig. 1) containing the chiral ligand 2-(*o*-diphenylphosphinophenyl)-3-*tert*-butyloxazoline, which has been shown by Pfaltz to be able to provide very high asymmetric inductions in the hydrogenation of a wide variety of unfunctionalized olefins.[20]

Preliminary experiments carried out at 100 °C under 50 atm of hydrogen showed that under these conditions the carbon–carbon double bond is quantitatively hydrogenated furnishing acid **3** with a fairly good enantioselectivity (66% ee, see Table 1).[21]

On lowering the reaction temperature at 60 or 30 °C, the substrate conversion remains complete, but the enantioselectivity does not increase. More adversely, when the reaction temperature is further lowered, the asymmetric induction drops dramatically. A decrease of the enantioselectivity on lowering the reaction temperature is quite unusual; however, it seems to be somewhat peculiar when using catalysts such as **Ir-PHOX** since an alike behaviour has been reported by Pfaltz.[23] No product racemization occurs as shown by an experiment carried out over 24 h (entry 6 of Table 1).

On decreasing the hydrogen pressure the asymmetric induction increases (Table 2) whatever the reaction temperature; the effect is stronger at lower temperatures;

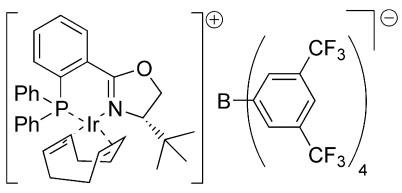

Figure 1. Ir-PHOX.

Table 1. Hydrogenation of **2** with of **Ir-PHOX**: influence of the temperature[a]

Entry	*T* (°C)	*t* (h)	ee[b] (%)
1	100	2	66[c]
2	60	2	66[c]
3	30	2	64[c]
4	0	2	46[c]
5	−20	2	27[c]
6	30	24	66[c]

[a] Reaction conditions. Substrate: 0.57 mmol; cat.: 2.27×10^{-2} mmol; solvent: dichloromethane (15 mL); $P(H_2)$: 50 atm; in all the experiments the substrate conversion is complete.
[b] The ees were determined by chiral GLC (on the methyl ester using Chiraldex G-TA column).
[c] Configuration of the prevailing enantiomer: (*R*) by polarimetry see Ref. 22.

thus, it appears that the hydrogen pressure is the most important parameter in determining the asymmetric induction (e.g., compare entries 4, 7 and 10 in Table 2).

This behaviour is in keeping with the Pfaltz's observation that terminal olefins react with a higher enantioselectivity at lower hydrogen pressures.[24]

Aiming at broadening our investigations with other transition-metal catalysts some experiments were carried out in the presence of the commercially available $[Rh(COD)(S)\text{-BINAP}]^+ClO_4^-\cdot THF$ (Aldrich).

Unfortunately, preliminary tests carried out in CH_2Cl_2 at 23 °C under 20 atm of hydrogen showed that while the hydrogenation proceeds with acceptable rates, no asymmetric induction is obtained.

The best results were obtained with a ruthenium catalytic system prepared in situ[25] by reacting $[Ru(benzene)Cl_2]_2$ with a chiral atropisomeric diphosphine (ligand:complex = 2:1 molar ratio) (see Table 3).

Indeed, the hydrogenation of **2** in the presence of the $[Ru(benzene)Cl_2]_2$/(*S*)-BINAP catalyst at 0 °C and

Table 2. Hydrogenation of **2** with **Ir-PHOX**: effect of the hydrogen pressure[a]

Entry	*T* (°C)	$P(H_2)$ (atm)	ee[b] (%)
1	60	100	61[c]
2	60	50	66[c]
3	60	10	76[c]
4	60	2	81[c]
5	30	50	64[c]
6	30	10	79[c]
7	30	2	80[c]
8	0	50	46[c]
9	0	10	75[c]
10	0	2	80[c]

[a] Reaction conditions. Substrate: 0.57 mmol; cat.: 2.27×10^{-2} mmol; solvent: dichloromethane (15 mL); time: 2 h; in all the experiments the substrate conversion is complete.
[b] The ees were determined by chiral GLC (on the methyl ester using Chiraldex G-TA column).
[c] Configuration of the prevailing enantiomer: (*R*) by polarimetry see Ref. 22.