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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9261–9265

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

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Received 3 August 2006; revised 25 October 2006; accepted 25 October 2006

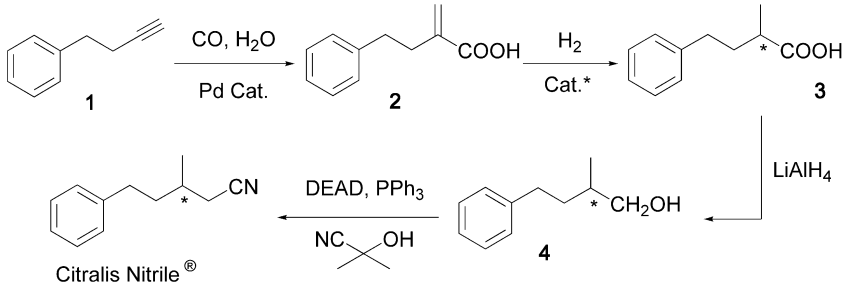
Abstract—A catalytic approach to the enantioselective synthesis of Citralis Nitrile® (3-methyl-5-phenyl-pentanenitrile, a citrus-type odorant) is described. The key step is the transition-metal catalyzed asymmetric hydrogenation of 2-phenethylacrylic acid. Among the different catalysts tested, the most 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®.

Keywords: Acrylic acids; Enantioselective hydrogenation; Atropisomeric diphosphine; Ruthenium; Iridium; Fragrance chemistry; Citralis Nitrile®.
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doi:10.1016/j.tetlet.2006.10.129

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;

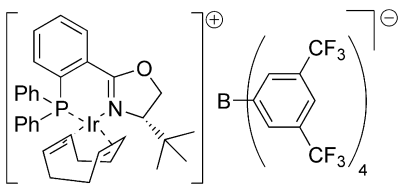

Figure 1. Ir-PHOX.

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.

Table 3. Hydrogenation of **2** in the presence of the Ru/atropisomeric diphosphine system[a]

Entry	Ligand	Promoter	T (°C)	t (h)	$P(H_2)$ (atm)	Conv. (%)	ee (%)[b]
1	(*S*)-BINAP	—	0	24	100	26	35[c]
2	(*S*)-BINAP	Et_3N	0	24	100	100	85[c]
3	(*S*)-BINAP	Et_3N	−20	24	100	100	88[c]
4	(*R*)-MeOBIPHEP	—	0	24	100	27	63[d]
5	(*R*)-MeOBIPHEP	Et_3N	0	24	80	100	88[d]
6	(*R*)-MeOBIPHEP	Et_3N	0	24	100	100	96[d]
7	(*R*)-MeOBIPHEP	Et_3N	0	24	130	100	98[d]
8	(*R*)-MeOBIPHEP	Et_3N	−20	24	80	100	96[d]

[a] Reaction conditions. Substrate: 2.84 mmol; $[Ru(benzene)Cl_2]_2$: 0.018 mmol; ligand: 0.036 mmol; solvent: methanol (10 mL).
[b] The ees were determined by chiral GLC (on the methyl ester using Chiraldex G-TA column).
[c] Configuration of the prevailing enantiomer: (*S*).
[d] Configuration of the prevailing enantiomer: (*R*).

under 100 atm of hydrogen proceeds quite slowly furnishing **3** with only a moderate enantioselectivity (35%, entry 1 of Table 3); however, when the same experiment is performed using triethylamine (1 equiv with respect to the substrate)[26] as the promoter, a remarkable increase of both the rate and the enantioselectivity (ee 85%) of the reaction is observed (entry 2 of Table 3). A further small improvement on the enantioselectivity (ee 88%) can be obtained working at −20 °C.

At present, we have no rationalization for the promoting effect played by triethylamine. As far as the increase in the rate is concerned, likely the base promotes the reaction by removing the HCl which forms owing to the heterolytic hydrogen activation on ruthenium.[27] As far as the increase in enantioselectivity is concerned, a simple explanation is that the amine transforms the acid substrate in the conjugated base allowing a stronger interaction with the metal centre; however, such hypothesis should be supported by a larger body of experimental evidences. It is worth to note that the promoting effect of bases in olefin hydrogenation in the presence of chiral ruthenium catalysts has been already described. In particular, Chan claims a useful promoting effect of amines in the asymmetric hydrogenation of α-arylpropenoic acids,[28] instead Noyori reports that t-C_4H_9OK strongly enhances the catalytic activity of certain ruthenium complexes in the asymmetric hydrogenation of α-ethylstyrene derivatives.[29] The promoting effect of triethylamine is observed also when the atropisomeric diphosphine (*R*)-MeOBIPHEP (Fig. 2)[30] is employed instead of (*S*)-BINAP (compare entries 4 and 6 in Table 3).

In the hydrogenation of **2**, (*R*)-MeOBIPHEP appears as a ligand distinctly more efficient than BINAP affording under the same conditions higher asymmetric inductions. As usual in the presence of ruthenium catalysts, both the hydrogen pressure and the reaction temperature influence the enantioselectivity. Indeed, at 0 °C on increasing the hydrogen pressure from 80 to 130 atm the enantioselectivity increases from 88% to 98% (entries 5–7 of Table 3) and keeping the hydrogen pressure constant at 80 atm on decreasing the reaction temperature from 0 °C to −20 °C, the enantioselectivity increases from 88% up to 96%.

Upon treatment with $LiAlH_4$[31] a sample of (*R*)-**3**[22] (ee 96%, $[\alpha]_D^{25}$ −28.0 (neat)) afforded (*R*)-2-methyl-4-phenylbutan-1-ol **4** (81% yield) having the same enantiomeric purity (ee 96% by chiral GC,[32] $[\alpha]_D^{25}$ +19.1 (*c*, 5.0, $CHCl_3$)[33]); the so obtained alcohol was reacted with acetone cyanohydrin in the presence of diethyl azodicarboxylate and PPh_3 (Mitsunobu conditions)[11] to afford Citralis Nitrile® **5** (73% yield, (*R*)-3-methyl-5-phenylpentanenitrile,[34] ee 96% by chiral GC,[35] $[\alpha]_D^{25}$ −2.35 (*c*, 2.2, EtOH)) without the loss of enantiopurity.

In conclusion, we have found a highly enantioselective and convenient catalytic system for the asymmetric hydrogenation of acrylic acid **2**. Using this catalytic system we have been able to synthesize almost enantiomerically pure Citralis Nitrile®. A practical application of this process would require the development of a convenient synthesis of alkyne **1**. Otherwise, an alternative route to the key acid **2**, such as a Mannich reaction on 2-phenylethylmalonic acid,[36,37] could be employed. More economically feasible and environmentally friendly processes, such as the catalytic hydrogenation[38] of **3** to give **4** and the direct conversion of alcohol **4** to the nitrile,[39] are also to be adopted for an industrial application.

Further studies aimed at improving the asymmetric hydrogenation rate and gathering more information on the catalytic cycle are in progress.

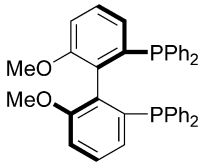

Figure 2. (*R*)-MeOBIPHEP.

Acknowledgements

We are indebted to the reviewers for helpful comments and suggestions. Rhodia UK Ltd—Phosphorus Specialties and Derivatives is acknowledged for generously supplying the BINAP ligand. The work has been performed with the Financial Support of the MIUR (Cofin 2004).

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21. **Ir-PHOX** catalyzed hydrogenation of **2**: In a typical experiment (entry 2 of Table 1), a magnetically stirred 150 mL stainless steel autoclave was charged, under an inert atmosphere, with 15 mL of CH_2Cl_2, 100 mg (0.57 mmol) of 2-phenethylacrylic acid, 35 mg (0.023 mmol) of **Ir-PHOX**, then pressurized with H_2 (50 atm) and heated to 60 °C. After 2 h, the crude product was concentrated and the residue filtered on a short silica column (eluent: diethyl ether/pentane 1:1) to give (*R*)-2-methyl-4-phenylbutyric acid as a colourless liquid (ee 66%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (d, $J = 7.0$ Hz, 3H, CH_3), 1.79 (m, 1H, CH_2), 2.07 (m, 1H, CH_2), 2.60 (m, 1H, CH), 2.72 (t, $J = 8.0$ Hz, 2H, CH_2), 7.19–7.48 (m, 5H, arom), 11.61 (br s, 1H, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.0$, 33.4, 35.2, 38.9, 126.0, 128.5, 141.5, 183.1. After conversion of the acid to the methyl ester, the ee was determined by Chiral GLC (Chiraldex GTA column (0.25 mm × 50 m); nitrogen flow 3.5 mL/min; $T = 93$ °C; $t_R = 81.26$ min (*R*), 82.65 (*S*)).
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2.65 (m, 2H, CH_2), 7.14–7.35 (m, 5H, arom). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.3$, 24.4, 29.8, 33.0, 37.4, 118.6, 126.0, 128.2, 128.4, 141.3.

35. The ee of nitrile **5** was determined by chiral GC: Chiraldex GTA column (0.25 mm × 50 m); nitrogen flow 3.5 mL/min; $T = 120$ °C; $t_R = 64.30$ (*S*), 65.25 (*R*).
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