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Hydroformylation of aryloxy ethylenes by Rh/BINAPHOS complex Catalyst deactivation path and application to the asymmetric synthesis of 2-aryloxypropanoic acids

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Abstract

The behavior of Rh(I)/(*S*,*R*)-BINAPHOS complex in the asymmetric hydroformylation of styrene and other aryloxy substituted ethylenes shows a sharp deterioration in stereocontrol as the conversion increases. This failure is apparently due to an irreversible reaction of the starting complex with the aldehyde which is built up in solution and its extent can be limited operating at short contact times and low temperatures. Under optimized conditions, the hydroformylation of aryloxy substituted ethylenes provides the relevant branched aldehyde in some 70% regioselectivity and in up to 80% ee.

Keywords: Enantioselective catalysis; Hydroformylation; Agrochemicals; Rhodium; BINAPHOS

1. Introduction

As the biological activity of chiral agrochemicals is in most cases dependent on the absolute configuration of the substrate [1–4], the use of racemic mixtures is commercially wasteful and increases the environmental burden to an unacceptable extent.

The herbicidal activity of 2-aryloxypropanoic acids, a class of agrochemicals of wide utility, resides exclusively in the (*R*)-enantiomer [4]. Chiral 2-arylpropionaldehydes, which are obvious precursors of 2-arylpropanoic acids, are easily accessible by Rh-catalyzed asymmetric hydroformylation of arylsubstituted ethylenes.

Asymmetric hydroformylation is one of the most important metal-catalyzed reactions, which provides an efficient synthetic tool for the transformation of cheap olefins into valuable chiral aldehydes through the formation of a new C–C bond. In spite of the great deal of work in this area and of the enormous synthetic potential of this reaction, few examples of Rh-catalyzed hydroformylation of olefins have demonstrated a high efficiency in the enantioselective variant of the reaction [5].

The most significant contribution in the field of enantioselective hydroformylation was given by Takaya, Nozaki and co-workers with the discovery of the BINAPHOS ligand. The hydroformylation of a wide variety of olefins with rhodium(I) complexes containing this chiral modifier or the related BIPHEMPHOS provides consistently high regio- and enantioselectivity under relatively mild conditions [6–11]. More recently, some other chiral bidentate phosphorus ligands have emerged as efficient chiral modifiers for Rh(I)-catalysts in the asymmetric hydroformylation of styrene [12–14] and high stereoselectivities have been

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obtained in the asymmetric hydroformylation of vinyl acetate using a chiral Rh(I)-catalyst with a bis(diazophospholidine) ligand [15]. With styrene, however, this last catalyst provides the branched aldehyde in low yield and in racemic form. In spite of these advances, no practical application of asymmetric hydroformylation to the synthesis of chiral fine chemicals is reported in the technical literature to date.

A few years ago, some of us reported that phenyl vinyl ethers can be effectively hydroformylated by rhodium carbonyl complexes with sterically hindered chiral diphosphites or ferrocenyldiphosphines, albeit in very low enantioselectivity [16]. Pursuing our work in this field, we have decided to focus our attention on the synthesis of *Mecoprop* and *Dichlorprop* [17] (Fig. 1). These are two herbicides of wide use of the family of aryloxypropanoic acids, which feature electron-withdrawing substituents on the phenyl ring.

Since Rh(I)/BINAPHOS has found to date the widest application in Rh-catalyzed asymmetric hydroformylation of aryl ethylenes, our first choice was to exploit this catalyst for our purpose. While a large number of olefins have been hydroformylated with this catalyst, the use of enol ethers as prochiral substrates has quite a few precedents [16,18] and, to the best of our knowledge, none of them employ BINAPHOS as the chiral ligand.

The results obtained in this study and some comments on the stability of the Rh(I)/BINAPHOS catalyst under the reaction conditions are reported in this paper.

2. Experimental

2.1. General methods and chemicals

(a*R*)-(+)-1,1′-binaphthalene-2,2′-diol ((*R*)-BINOL), (a*S*)-(+)-1,1′-binaphthalene-2,2′-diol ((*S*)-BINOL), $Rh(CO)_2$(acac), $[Rh(COD)Cl]_2$, phenol, 2,4-dichlorophenol, 2-methyl-4-chlorophenol, 1,2-dibromoethane and styrene were of commercial quality and used as purchased or after further purification. BINAPHOS was prepared according to literature procedure [6]. Phosphorus trichloride (PCl_3) was distilled before use and stored under argon atmosphere. Triethylamine (Et_3N) was distilled over KOH. All reactions were carried out under a positive pressure of argon. Toluene was used freshly distilled over sodium.

^1H NMR and ^{31}P NMR spectra were recorded with a Varian VXR 5000 spectrometer at 299.94 and 121.42 MHz, respectively. ^{31}P NMR chemical shifts are relative to H_3PO_4 (external standard) in $CDCl_3$. Mass spectra were recorded using a HP 5971 series mass spectrometer. Elemental analyses were performed using an elemental analyzer Perkin Elmer model 240 C. Optical rotations were measured with a Perkin Elmer 241 spectropolarimeter. The purity of all compounds was judged to be >98% by ^1H NMR and ^{31}P NMR spectral determination.

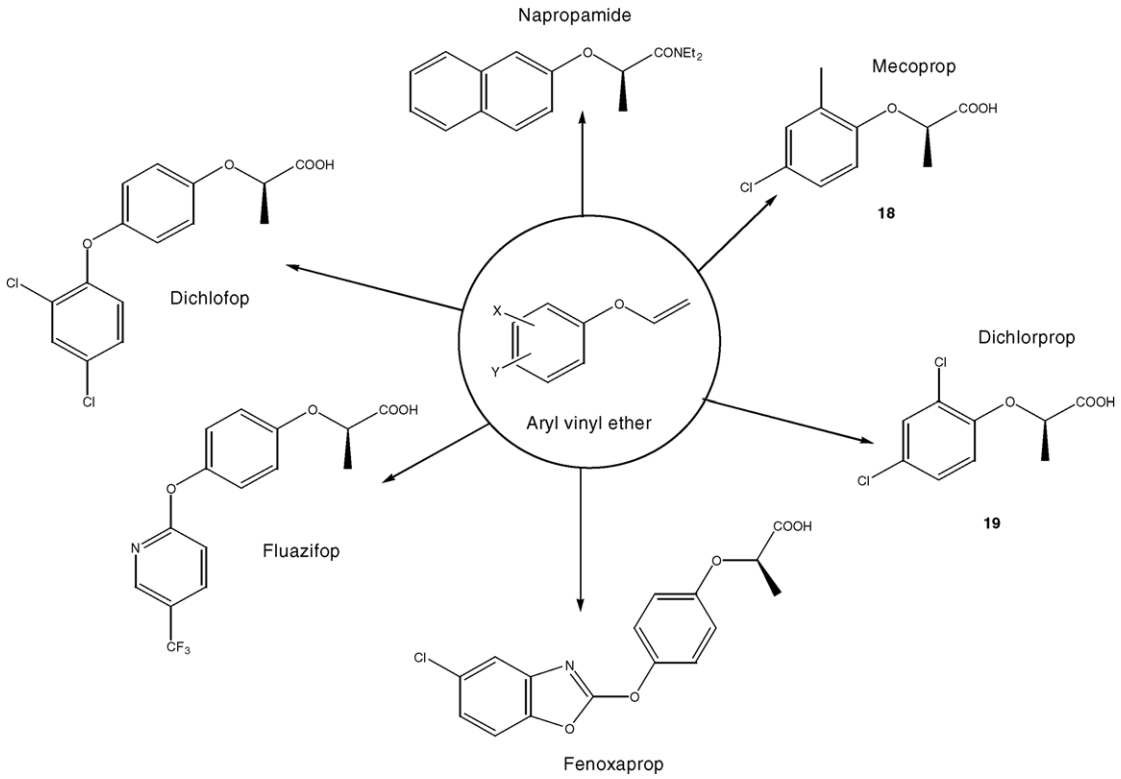


Fig. 1. Example of chiral agrochemicals, possible target molecules for the enantioselective hydroformylation of the corresponding aryl vinyl ethers.

2.2. Hydroformylation of styrene

A 150 mL stainless steel reaction vessel was charged under argon purge with 10 mmol of the substrate, 0.005 mmol of $Rh(CO)_2(acac)$, 0.02 mmol of BINAPHOS and 10 mL of anhydrous toluene. The reactor was then pressurized to 80 atm with synthesis gas ($CO/H_2 = 1$) and heated at 60 °C. At several reaction times, samples were collected from the reaction mixture through a stainless steel capillary built for this purpose. Each sample was analyzed by GC–MS and by chiral GC to determine simultaneously conversion, chemoselectivity, regioselectivity and enantioselectivity.

2.3. General procedures for the synthesis of aryl vinyl ethers

2.3.1. Phenyl vinyl ether (**1**)

A mixture of 1,2-dibromoethane (46.1 g, 0.24 mol) and phenol (15.0 g, 0.16 mol) in H_2O (80 mL) was stirred and heated to reflux temperature in a 500 mL three-neck flask equipped with a mechanical stirrer, reflux condenser and dropping funnel. After half an hour, a solution of NaOH (8.56 g, 0.21 mol) in H_2O (52 mL) was added dropwise. After the addition of all the NaOH solution, the reaction mixture was refluxed for 16 h. The mixture was then cooled, the organic layer was separated and the aqueous phase extracted several times with CH_2Cl_2. The organic extracts were washed with a diluted aqueous NaOH solution, then with H_2O and finally dried over anhydrous Na_2SO_4. After evaporation in vacuo of the solvent and the excess of 1,2-dibromoethane, the resultant crude 1-phenoxy-2-bromoethane (25.7 g) was sufficiently pure (GC) to be used in the following dehydrohalogenation reaction.

A solution of crude 1-phenoxy-2-bromoethane (25.7 g) in dry benzene (75 mL) was slowly added to a refluxing potassium *t*-butoxide solution over a period of 6 h. After cooling to room temperature, the solution was diluted with H_2O (150 mL) and extracted several times with Et_2O. After removing the solvent under vacuum, the residue was distilled at reduced pressure: bp 54–55 °C (10 mmHg) giving phenyl vinyl ether (12 g, 0.1 mol, 62% overall yield). Mass spectra: EI (70 eV) *m/z*: 121 $[M+1]^+$, 120 $[M]^+$, 77 $[C_6H_5]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.45–6.97 (m, 5H, Ar), 6.71 (dd, $^1J = 13.2$ Hz, $^2J = 6.7$ Hz, 1H,), 4.85 (dd, $^1J = 13.2$ Hz, $^2J = 1.6$ Hz, 1H), 4.50 (dd, $^1J = 6.7$ Hz, $^2J = 1.6$ Hz, 1H).

Following the above described procedure, 4-chlorophenyl vinyl ether (**2**), 2-methyl-4-chlorophenyl vinyl ether (**3**), 2,4-dichlorophenyl vinyl ether (**4**) and 4-phenoxy-phenyl vinyl ether (**5**) were prepared in 60, 58, 64 and 52% overall yields, respectively.

2.3.2. 4-Chlorophenyl vinyl ether (*2*)

Boiling point 130–131 °C at 10 mmHg; mass spectra: EI (70 eV) *m/z*: 157 $[M+2]^+$, 155 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.22 (d, $J = 9.4$ Hz, 2H, Ar), 6.94 (d, $J = 9.4$ Hz, 2H, Ar), 6.58 (dd, $^1J = 15.7$ Hz, $^2J = 3.1$ Hz, 1H), 4.78 (dd, $^1J = 15.7$ Hz, $^2J = 1.1$ Hz, 1H), 4.42 (dd, $^1J = 3.1$ Hz, $^2J = 1.1$ Hz, 1H).

2.3.3. 2-Methyl-4-chlorophenyl vinyl ether (*3*)

Boiling point 92 °C at 5 mmHg; mass spectra: EI (70 eV) *m/z*: 170 $[M+2]^+$, 168 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.30–6.83 (m, 3H, Ar), 6.59 (dd, $^1J = 15.8$ Hz, $^2J = 6.8$ Hz, 1H), 4.63 (dd, $^1J = 15.8$ Hz, $^2J = 1.4$ Hz, 1H), 4.40 (dd, $^1J = 6.8$ Hz, $^2J = 1.4$ Hz, 1H), 2.25 (s, 3H).

2.3.4. 2,4-Dichlorophenyl vinyl ether (*4*)

Boiling point 104 °C at 10 mmHg; mass spectra: EI (70 eV) *m/z*: 190 $[M+2]^+$, 188 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.47–6.94 (m, 3H, Ar), 6.56 (dd, $^1J = 13.9$ Hz, $^2J = 6.9$ Hz, 1H,), 4.76 (dd, $^1J = 13.9$ Hz, $^2J = 1.8$ Hz, 1H), 4.53 (dd, $^1J = 6.9$ Hz, $^2J = 1.8$ Hz, 1H).

2.3.5. 4-Phenoxyphenyl vinyl ether (*5*)

Boiling point 138–140 °C at 10 mmHg; mass spectra: EI (70 eV) *m/z*: 212 $[M]^+$, 77 $[C_6H_5]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.38–6.91 (m, 9H, Ar), 6.62 (dd, $^1J = 15.8$ Hz, $^2J = 4.7$ Hz, 1H), 4.65 (dd, $^1J = 15.8$ Hz, $^2J = 1.4$ Hz, 1H), 4.38 (dd, $^1J = 4.7$ Hz, $^2J = 1.4$ Hz, 1H).

2.4. General procedure for the hydroformylation of aryl vinyl ethers

A 150 mL stainless steel reaction vessel was charged under argon purge with 5 mmol of substrate, 0.01 mmol $Rh(CO)_2(acac)$, 0.04 mmol (*S*,*R*)-BINAPHOS and 10 mL anhydrous toluene. The reaction was carried out at 60 °C and 80 atm (synthesis gas $CO/H_2 = 1$), for 48 h. At the end of the reaction the crude reaction mixture was analyzed by chiral GC (see Section 2.1) to determine simultaneously conversion, chemo-, regio- and enantioselectivity. From the reaction mixture, the aldehydes were purified by flash chromatography on silica gel using a 9:1 hexane/ethyl acetate mixture as eluent.

The aldehydes obtained, 2-phenoxypropanal (**6**), 3-phenoxypropanal (**11**), 2-(4-chlorophenoxy)propanal (**7**), 3-(4-chlorophenoxy)propanal (**12**), 2-(2-methyl-4-chlorophenoxy)propanal (**8**), 3-(2-methyl-4-chlorophenoxy)propanal (**13**), 2-(2,4-dichlorophenoxy)propanal (**9**), 3-(2,4-dichlorophenoxy)propanal (**14**), 2-(4-phenoxylphenoxy)propanal (**10**), 3-(4-phenoxylphenoxy)propanal (**15**) gave ^{1}H NMR patterns consistent with their structures.

2.4.1. 2-Phenoxypropanal (*6*)

Boiling point 88–90 °C at 10 mmHg; mass spectra: EI (70 eV) *m/z*: 151 $[M+1]^+$, 150 $[M]^+$, 77 $[C_6H_5]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.64 (d, $J = 1.8$ Hz, 1H), 7.40–6.67 (m, 5H, Ar), 4.52 (q, $J = 5.8$ Hz, 1H), 1.46 (d, $J = 5.8$ Hz, 3H).

2.4.2. 3-Phenoxypropanal (*11*)

Boiling point 91–93 °C at 10 mmHg; mass spectra: EI (70 eV) *m/z*: 151 $[M+1]^+$, 150 $[M]^+$, 77 $[C_6H_5]^+$. ^{1}H NMR

($CDCl_3$), δ (ppm): 9.74 (t, J = 1.7 Hz, 1H), 7.35–6.65 (m, 5H, Ar), 4.18 (t, J = 4.8 Hz, 2H), 2.75 (t, J = 4.8 Hz, 2H).

2.4.3. 2-(4-Chlorophenoxy)propanal (7)

Boiling point 84–86 at 1 mmHg; mass spectra: EI (70 eV) m/z: 186 $[M+2]^+$, 184 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.61 (d, J = 1.7 Hz, 1H), 7.20 (d, J = 9.1 Hz, 2H, Ar), 6.91 (d, J = 9.1 Hz, 2H, Ar), 4.48 (q, J = 5.5 Hz, 1H), 1.43 (d, J = 8.3 Hz, 3H).

2.4.4. 3-(4-Chlorophenoxy)propanal (12)

Boiling point 87–90 °C at 1 mmHg; mass spectra: EI (70 eV) m/z: 186 $[M+2]^+$, 184 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.71 (t, J = 1.5 Hz, 1H), 7.18 (d, J = 8.9 Hz, 2H, Ar), 6.88 (d, J = 8.9 Hz, 2H, Ar), 4.16 (t, J = 4.8 Hz, 2H), 2.63 (t, J = 4.8 Hz, 2H).

2.4.5. 2-(2-Methyl-4-chlorophenoxy)propanal (8)

Boiling point 84–86 at 0.5 mmHg; mass spectra: EI (70 eV) m/z: 200 $[M+2]^+$, 198 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.60 (d, J = 1.6 Hz, 1H), 7.38–6.46 (m, 3H, Ar), 4.51 (q, J = 8.3 Hz, 1H), 2.23 (s, 3H), 1.43 (d, J = 8.3 Hz, 3H).

2.4.6. 3-(2-Methyl-4-chlorophenoxy)propanal (13)

Boiling point 87–89 °C at 0.5 mmHg; mass spectra: EI (70 eV) m/z: 200 $[M+2]^+$, 198 $[M]^+$, 77 $[C_6H_5]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.78 (t, J = 1.4 Hz, 1H), 7.34–6.42 (m, 3H, Ar), 4.18 (t, J = 6.4 Hz, 2H), 2.75 (dt, ^1J = 6.4 Hz, ^2J = 1.4 Hz, 2H), 2.31 (s, 3H).

2.4.7. 2-(2,4-Dichlorophenoxy)propanal (9)

Melting point 62–65 °C; mass spectra: EI (70 eV) m/z: 220 $[M+1]^+$, 219 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.69 (d, J = 1.3 Hz, 1H), 7.40–6.63 (m, 3H, Ar), 4.54 (q, J = 9.8 Hz, 1H), 1.45 (d, J = 9.8 Hz, 3H).

2.4.8. 3-(2,4-Dichlorophenoxy)propanal (14)

Melting point 60–65 °C; mass spectra: EI (70 eV) m/z: 220 $[M+1]^+$, 219 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.98 (t, J = 1.4 Hz, 1H), 7.42–6.65 (m, 3H, Ar), 4.22 (t, J = 8.5 Hz, 2H), 2.83 (t, J = 8.5 Hz, 2H).

2.4.9. 2-(4-Phenoxyphenoxy)propanal (10)

Boiling point 120–122 °C at 1 mmHg; mass spectra: EI (70 eV) m/z: 242 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.64 (d, J = 1.1 Hz, 1H), 7.20–6.80 (m, 9H, Ar), 4.50 (q, J = 5.0 Hz, 1H), 1.42 (d, J = 5.0 Hz, 3H).

2.4.10. 3-(4-Phenoxyphenoxy)propanal (15)

Boiling point 123–125 °C at 1 mmHg; mass spectra: EI (70 eV) m/z: 242 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.71 (t, J = 1.2 Hz, 1H), 7.20–6.80 (m, 9H, Ar), 4.24 (t, J = 5.2 Hz, 2H), 2.81 (t, J = 5.2 Hz, 2H).

2.5. General procedure for the oxidation of oxo-aldehydes to the corresponding carboxylic acids

To a solution of the oxo-aldehyde (4.7 mmol) in acetonitrile (5.6 mL), NaH_2PO_4 (152 mg) in H_2O (2.2 mL) and H_2O_2 35% (0.5 mL) was added a solution of $NaClO_2$ (0.72 g, 6.3 mmol) in H_2O (6.3 mL) at 10 °C. During the reaction (about 2 h) oxygen was evolved and monitored with a bubbler connected to the apparatus. At the end of the reaction, Na_2SO_3 (60 mg) was added to destroy the unreacted HOCl and H_2O_2. The reaction mixture was then acidified with 10% aqueous HCl, extracted with Et_2O and the extracts dried over Na_2SO_4. The acids were obtained in 80–85% yield and were purified by transformation into their sodium salts. Compounds **16**, **18** and **19** were consistent with reported literature data [16]. Compounds **17** and **20** were characterized by ^{1}H NMR.

2.6. Determination of optical purity and enantiomeric excesses of 2-aryloxypropanoic acids

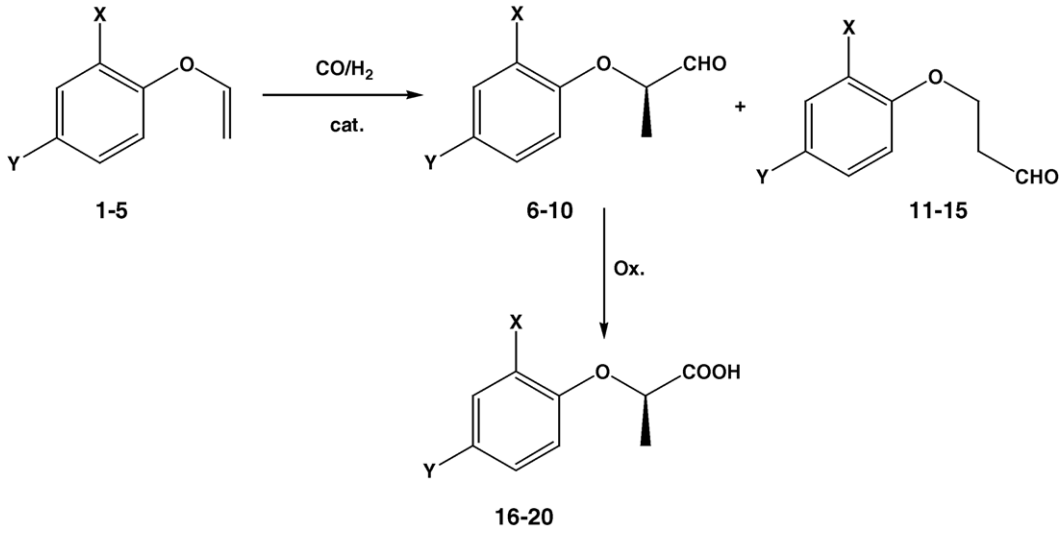
The optical purity and the absolute configurations of the acids **16**, **18** and **19** were determined on the basis of the specific rotations reported in the literature [19–21] and the enantiomeric excesses were confirmed by chiral HPLC. The HPLC analyses were performed using a HPLC chromatograph equipped with UV detector and a Chiracel OD chiral column (25 × 4.6 i.d.), using *n*-hexane/2-propanol/formic acid 90:10:1 as eluent at 0.5 mL/min flow rate. Separation factors α were >1.35. The difference between the values of optical purity and ee are small (2–5%). The specific rotations of the acids **17** and **20** were not available from the literature. Their ee values were determined by chiral HPLC.

The enantiomeric excesses of the aldehydes **6**–**10** were determined by chiral GC using a gas chromatograph Perkin Elmer model 8500 equipped with a 25 m capillary column (DEtTbuSilBETACDX). The ee of the acids determined by HPLC are in keeping with the ee of the corresponding aldehydes as determined by chiral GC.

3. Results and discussion

The aryl vinyl ethers **1**–**5** to be used as starting materials for this investigation were prepared by dehydrohalogenation of the corresponding 1-aryloxy-2-bromoethane with potassium *tert*-butoxide in benzene (Scheme 1). The intermediate bromo ether was obtained by alkylation of the suitable phenol with 1,2-dibromoethane (see Section 2).

4-Chloro-2-methyl-1-vinyloxy-benzene (**3**) and 2,4-dichloro-1-vinyloxy-benzene (**4**) were used as substrates for our investigation since the corresponding aldehydes are precursors of the commercial herbicides *Mecoprop* (**18**) and *Dichlorprop* (**19**) (Fig. 1). The outcomes of the first experiments were however disappointing since the hydroformylation of **3** and **4** produced the branched aldehyde almost



Scheme 1. Hydroformylation of functionalyzed aryl vinyl ethers catalyzed by Rh(I)/(*S*,*R*)-BINAPHOS. **1**, **6**, **11**, **16**. X = H, Y = H; **2**, **7**, **12**, **17**. X = H, Y = Cl; **3**, **8**, **13**, **18**. X = CH_3, Y = Cl; **4**, **9**, **14**, **19**. X = Cl, Y = Cl; **5**, **10**, **15**, **20**. X = H, Y = C_6H_5O.

racemic in modest yield. This prompted us to gain a deeper insight into the catalytic behavior of the rhodium complex modified with (*S*,*R*)-BINAPHOS ligand in the hydroformylation of styrene. When this reaction was repeated under conditions reported in the literature [6], a quantitative conversion was obtained, but the enantiomeric excesses were around 30%, lower than expected. In search of more details, we decided to monitor the profile of this reaction.

To this purpose, a range of experiments were run using the same conditions reported in the literature, but with different reaction times. The results of these experiments were broadly consistent with the literature data during the early stages of the reaction. After about 12 h, however the stereoselectivity of the reaction started to deteriorate and decreased steadily from 95% ee to 33% ee after 47 h (Table 1).

This undesired result is thought to be a consequence of degradation of the catalyst caused by the increasing concentration of the aldehyde in the reaction mixture [22]. This may result in the formation of different rhodium complexes, still active for the hydroformylation but with poor or no stereocontrol. Furthermore, we observe a strong decrease in enantiomeric excess at the end of the reaction, which cannot be completely accounted for by the increased production of racemic aldehyde (conversion increasing from 92 to 99%, see Table 1 and Fig. 2), but indicates that racemization of the aldehyde is also occurring.

These variations are accompanied by an improvement in the branched selectivity in the last part of the reaction from 87/13 to 91/9. This effect corresponds to a b/l ratio as high as 97/3 in the final part of the reaction. It may not be purely coincidental that this value closely agrees with the regioselectivity displayed by simple rhodium carbonyl hydrides in the hydroformylation of styrene under our conditions [23]. These results are shown graphically in Fig. 2 where the concentration of the branched aldehyde and the enantiomeric excess are plotted against the reaction time. The graph clearly shows a sharp discontinuity in the dependence of the enantioselec-

Table 1
Enantioselective hydroformylation of styrene catalyzed by Rh(I)/(*S*,*R*)-BINAPHOS at several reaction times

Reaction time (h)	Conversion (%)	Branched/linear	ee (%) (*S*)[a]
4	22	87/13	95
11	38	87/13	94
23	64	87/13	88
35	92	90/10	50
47	99	91/9	33

Reaction conditions: solvent = toluene; catalytic precursor $Rh(CO)_2(acac)$/(*S*,*R*)-BINAPHOS = 1:4; temperature = 60 °C; pressure = 80 atm (CO/H_2 = 1:1); substrate/catalyst = 2000:1. Ethyl benzene never exceeds 1%.
[a] Determined with chiral GC.

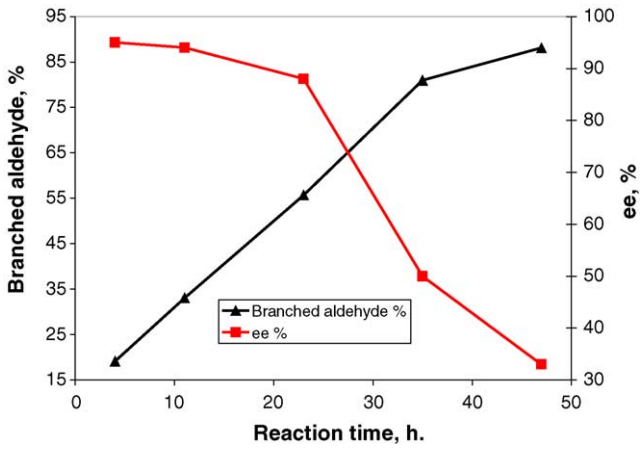


Fig. 2. Hydroformylation of styrene: time-dependent pathway of ee and branched aldehyde. Reaction conditions: solvent = toluene; pressure = 80 atm (CO/H_2 = 1:1); reaction time = 48 h; substrate to catalyst molar ratio = 2000:1; BINAPHOS/Rh = 4:1. No by-products were recorded.

Table 2
Enantioselective hydroformylation of aryl vinyl ethers catalyzed by $Rh(CO)_2(acac)$/(*S*,*R*)-BINAPHOS

Substrate	Conversion (%)	Branched/linear	ee (%);[a] (configuration)
1	52	65/35	65(*R*)
2	50	70/30	77[b]
3	56	63/37	80(*R*)
4	54	67/33	72(*R*)
5	35	71/29	65[b]

[a] Determined to the crude reaction mixture using chiral GC.
[b] Absolute configuration unknown. Most probably (*R*).

tivity after about 24 h and a similar but less pronounced effect for the regioselectivity.

As it is known that aldehydes can react with phosphites to produce phosphonates [22], the observed deactivation of Rh(I)/(*S*,*R*)-BINAPHOS may originate from this interaction. To get an insight into this process, we ran the hydroformylation of styrene with Rh(I)/(*S*,*R*)-BINAPHOS in the presence of racemic 2-phenyl propanal in order to model the conditions where the strongest decrease of ee occurs. A mixture made up with styrene, 2-phenyl propanal, $Rh(CO)_2(acac)$, (*S*,*R*)-BINAPHOS (1000/10/1/4 molar ratio) in toluene was stirred overnight at room temperature under nitrogen and then hydroformylated at 60 °C and 80 atm for 48 h. Complete conversion into a racemic mixture of aldehydes was obtained, suggesting that in the presence of a moderate concentration of aldehyde the rhodium complex is irreversibly transformed into a new catalytic species devoid of stereocontrol.

Since our interest was in the synthesis of chiral agrochemical precursors, we did not pursue the studies of racemization further, but instead we tried to exploit the above reported observations. Thus, aiming at high stereoselectivities, the hydroformylation of aryl vinyl ethers was stopped at about 50% conversion.

As apparent from Table 2, under these conditions, the selectivity towards the branched aldehyde is moderate (63–71%), while the enantioselectivity is fair to good (65–80% ee). To the best of our knowledge, these values are the highest ones obtained so far in the hydroformylation of these substrates. Since the oxidation of the branched aldehydes to the corresponding acids takes place without any racemization, this stereoselectivity corresponds to the enantiopurity of the agrochemical. Although the modest conversion and the poor branched to linear ratio limit the practical application of this approach, it should be pointed out that the value of 80% ee recorded with substrate **3** complies with the requirement suggested for the commercialization of agrochemicals in the form of single enantiomer.

4. Conclusions

The performance of the Rh(I)/(*S*,*R*)-BINAPHOS complex in the enantioselective hydroformylation of aryl ethylenes is critically affected by the poor stability of the catalyst. This seems related to an irreversible reaction undergone by the complex with the aldehyde which is built up in solution as the reaction proceeds. This reaction probably involves the phosphite moiety of the ligand and produces one or more new catalytic species devoid of stereocontrol on the reaction. These species are apparently able also to induce racemization of the chiral 2-phenylpropanal present in solution.

The extent of this undesired process is dependent on temperature and reaction time. Its detrimental consequences can be limited to some extent if the hydroformylation is run at low temperature and the conversion of the substrate is kept low. Under these optimized conditions, some phenyl aryl ethers **1** can be successfully hydroformylated and, thanks to the favorable regioselectivity (>2:1), they produce the relevant branched aldehydes **2** in fair chemical yields and in up to 80% ee. This result represents a substantial improvement over the previous methodologies in the preparation of these important intermediates and provides an indication of future direction for the asymmetric synthesis of the relevant acids.

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