Applied homogeneous catalysis by organometallic complexes

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The overview describes the industrial application of homogeneous catalysts for the chemical industry. In the first part, some theoretical background is given on organometallic complexes and homogeneous catalysis followed by a description of the prerequisites and current problems for their industrial application. Selected examples of industrially useful catalysts for the manufacture of bulk and fine chemicals are described for the following transformations: enantioselective hydrogenation, isomerization and epoxidation for producing enantiomerically enriched products; the application of the Heck reaction, the Suzuki and Sonogashira coupling and the carbonylation reaction for the manufacture of intermediates for pharmaceuticals and agrochemicals; the application of the carbonylation technology for the large-scale production of acetic acid and butyraldehydes. In the last part, future prospects of the industrial application of homogeneous catalysis are briefly discussed.

Where are homogeneous catalysts used?

The first industrial applications of organometallic complexes for catalysing chemical reactions were realized in the field of relatively simple, high volume chemical intermediates and polymers. This area of use is still growing and almost every year, new processes are introduced into production[1]. A new trend is the application of homogeneous catalysts for the synthesis and production of multifunctional, more complex molecules such as agrochemicals and pharmaceuticals[2]. This short overview will give some theoretical background explaining why organometallic complexes are such versatile catalysts and then will review three areas where the application of homogeneous catalysts has proven especially fruitful for the synthesis of relatively complex fine chemicals, namely enantioselective catalysis, C–C coupling and carbonylation reactions.

Some theory

What is an organometallic complex? Originally, these were defined as metal complexes with one or more metal–carbon bonds. Nowadays, metal complexes with ligands such as phosphines, hydrides or amines are also accepted as organometallics. In Figure 1 and Table 1 a number of important terms and properties of organometallic complexes are summarized. The central metal as well as the type of ligand determine the reactivity of such a complex, i.e. the ability to react with substrate molecules and eventually the capability to catalyse chemical transformations.

Why are such complexes able to catalyse reactions and accelerate the breaking and forming of chemical bonds without being consumed in the process? There are several reasons[3]. First of all, almost any molecule with a functional group can coordinate to a specific metal centre; upon coordination the reactivity of this functional group may change dramatically. Secondly, highly reactive species can be stabilized and react further in a controlled and productive way. Thirdly, two molecules can
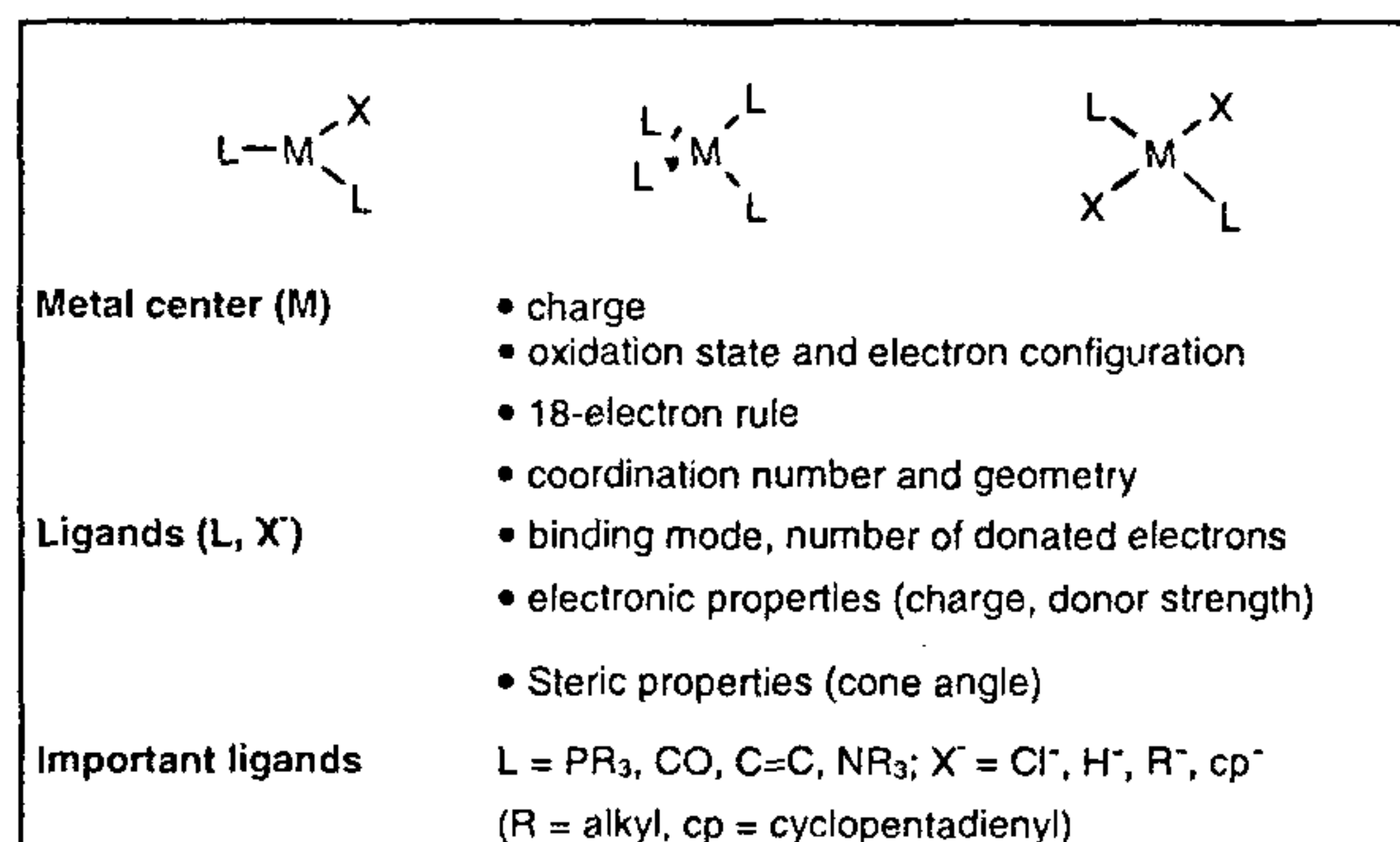
Metal center (M)	• charge
	• oxidation state and electron configuration
	• 18-electron rule
	• coordination number and geometry
Ligands (L, X⁻)	• binding mode, number of donated electrons
	• electronic properties (charge, donor strength)
	• Steric properties (cone angle)
Important ligands	L = PR₃, CO, C=C, NR₃; X⁻ = Cl⁻, H⁻, R⁻, cp⁻ (R = alkyl, cp = cyclopentadienyl)

Figure 1. Characteristics of organometallic complexes.

Table 1. Selected organometallic complexes, their geometry and preferred reactions

Metal, oxidation state	Example	Geometry	Preferred reactions
Ni⁰	Ni(CO)₄	Tetrahedral	Ligand dissociation
Pd⁰	Pd(PR₃)₂	Linear	Oxidative addition
Ni^II, Pd^II	ArPd(PR₃)₂X	Square planar	Reductive elimination
Rh^I, Ir^I	Rh(PR₃)₂X	Square planar	Oxidative addition
Ru^II	Ru(PR₃)₃X₂	Trigonal pyramid	Ligand dissociation, oxidative addition
Ru^II, Rh^III, Ir^III	Rh(PR₃)₃XH₂	Octahedral	Reductive elimination

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coordinate to the same metal centre leading through proximity to an enhanced probability of reaction. Last, but not least, the ligands present can exert some sort of control of the occurring reactions, leading to selective transformations.

On the other hand, catalytic reactions also have some drawbacks since some of the precursor complexes used as catalysts are often troublesome to prepare and handle due to their sensitivity and low stability. In addition, the presence of an organometallic catalyst enhances the complexity of a reaction and makes the reaction pathways much more difficult to understand. The synthetic organic chemist has to learn some new rules in order to interpret his results. However, organometallic chemists have found that most catalytic reactions can be described using a finite number of elementary steps (see Figure 2). Using kinetic as well as structural information, it is then often possible to postulate a sequence of such elementary steps that adequately explains the observed products.

Critical factors and current problems for the industrial application of homogeneous catalysts[4]

Prerequisites

Several important factors determine, whether the industrial use of a catalyst is economically feasible. For each individual transformation specific prerequisites must be
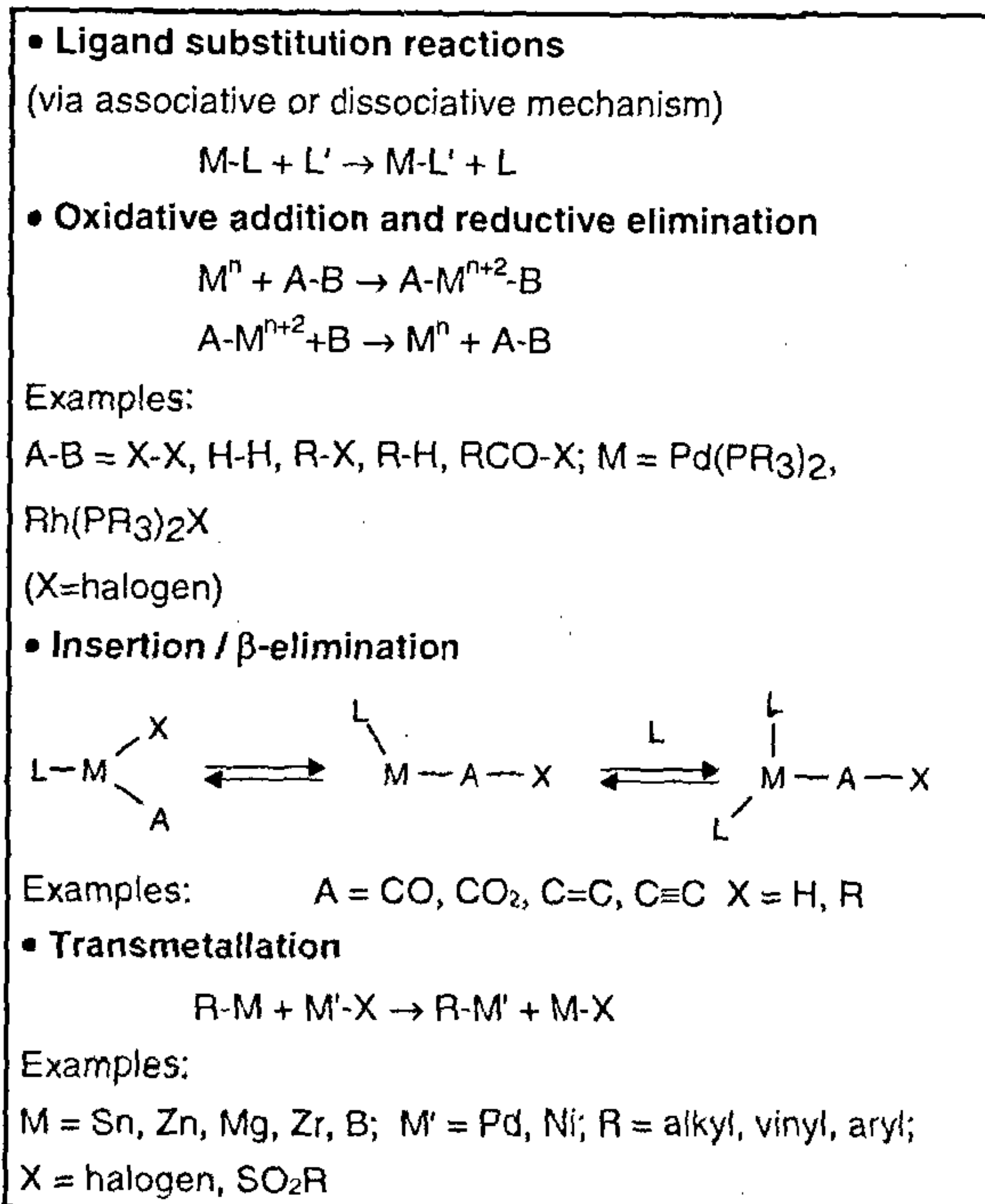
defined and when some of these are not met, either another catalyst has to be found or another route to the desired product must be developed.

One of the most important criteria for judging a catalyst is its **selectivity**, defined as the ratio of the desired product to the sum of all products. A high selectivity is essential for an economical as well as an ecological process. One can distinguish different types of selectivities:

- Chemoselectivity: The preferential reaction of one of the several potentially reactive functional groups.
- Regioselectivity: The preferential reaction at one of the several potentially reactive centres of a conjugated system.
- Stereoselectivity: The preferential formation of one of the several possible stereoisomers.
- Enantioselectivity: The preferential formation of one enantiomer (in this case, the selectivity is defined as enantiomeric excess (ee, %), as the difference between the per cent desired and per cent undesired enantiomer).

Another important factor is the **catalyst productivity**, defined as turnover number (ton), i.e. the number of moles product produced with one mole of catalyst. This number determines the catalyst costs. If a catalyst can be re-used, its productivity is increased.

The **catalyst activity**, often defined as turnover frequency (tof), i.e. how many moles of product one mole of the catalyst produces per time unit, determines the production capacity of a given apparatus.

In addition, other aspects such as availability and cost of ligands and metal precursors, catalyst stability and sensitivity, handling problems, catalyst separation, space time yield, poisoning of the catalytic system, chemoselectivity, process sensitivity, toxicity, safety, special equipment, etc. can be of importance when applying homogeneous catalysts.

Current problems

When an industrial catalytic process has to be developed, the following aspects and problems have to be solved. Sometimes, it is quite time-consuming to find viable solutions because catalysis is still a rather empirical science.

- Because academic research is often focused on selectivity as the only criterion, the search for a sufficiently high activity and productivity for promising literature catalysts and processes is a major task for the industrial chemist and often requires intensive process and sometimes catalyst development.
- Many catalyst precursors and ligands are very expensive, therefore a search for cheaper catalysts with the same performance is necessary.
- Most of the (chiral) ligands used in the literature are not available commercially or available only in small quantities. The development of a large-scale synthesis

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• **Ligand substitution reactions**

(via associative or dissociative mechanism)

$$M\text{-}L + L' \rightarrow M\text{-}L' + L$$

• **Oxidative addition and reductive elimination**

$$M^n + A\text{-}B \rightarrow A\text{-}M^{n+2}\text{-}B$$

$$A\text{-}M^{n+2} + B \rightarrow M^n + A\text{-}B$$

Examples:

A-B = X-X, H-H, R-X, R-H, RCO-X; M = Pd(PR$_3$)$_2$,

Rh(PR$_3$)$_2$X

(X=halogen)

• **Insertion / β-elimination**

Examples: A = CO, CO$_2$, C=C, C≡C   X = H, R

• **Transmetallation**

$$R\text{-}M + M'\text{-}X \rightarrow R\text{-}M' + M\text{-}X$$

Examples:

M = Sn, Zn, Mg, Zr, B; M' = Pd, Ni; R = alkyl, vinyl, aryl;

X = halogen, SO$_2$R

Figure 2. Important elementary steps in a catalytic reaction.

of these ligands has therefore to be part of the process development.

• In a multistep synthesis, care has to be taken that especially the preceding step is compatible with the catalytic step, e.g. no byproducts which could poison the catalyst are present (even in very small quantities).

• For homogeneous complexes, separation from the product solution is a problem without a general solution. Distillation or crystallization of the product are often very effective, sometimes, phase separation or extraction can be used successfully. Another approach is the immobilization of a soluble catalyst on an insoluble carrier that can be separated by filtration.

Enantioselective catalysis

Many molecules are chiral, i.e. they exist in two forms that have the same composition, connectivity and spatial arrangement of the atoms but are mirror images of each other that are not superimposable. Because the two enantiomeric molecules very often have different biological properties, the preferential synthesis of one enantiomer, called enantioselective synthesis, is desirable for pharmaceuticals, agrochemicals and flavours or fragrances. As depicted in Figure 3, a chiral auxiliary must be present, to be able to control the formation of the product in such a way that one enantiomer is formed preferentially. Enantioselective catalysis is especially attractive because the
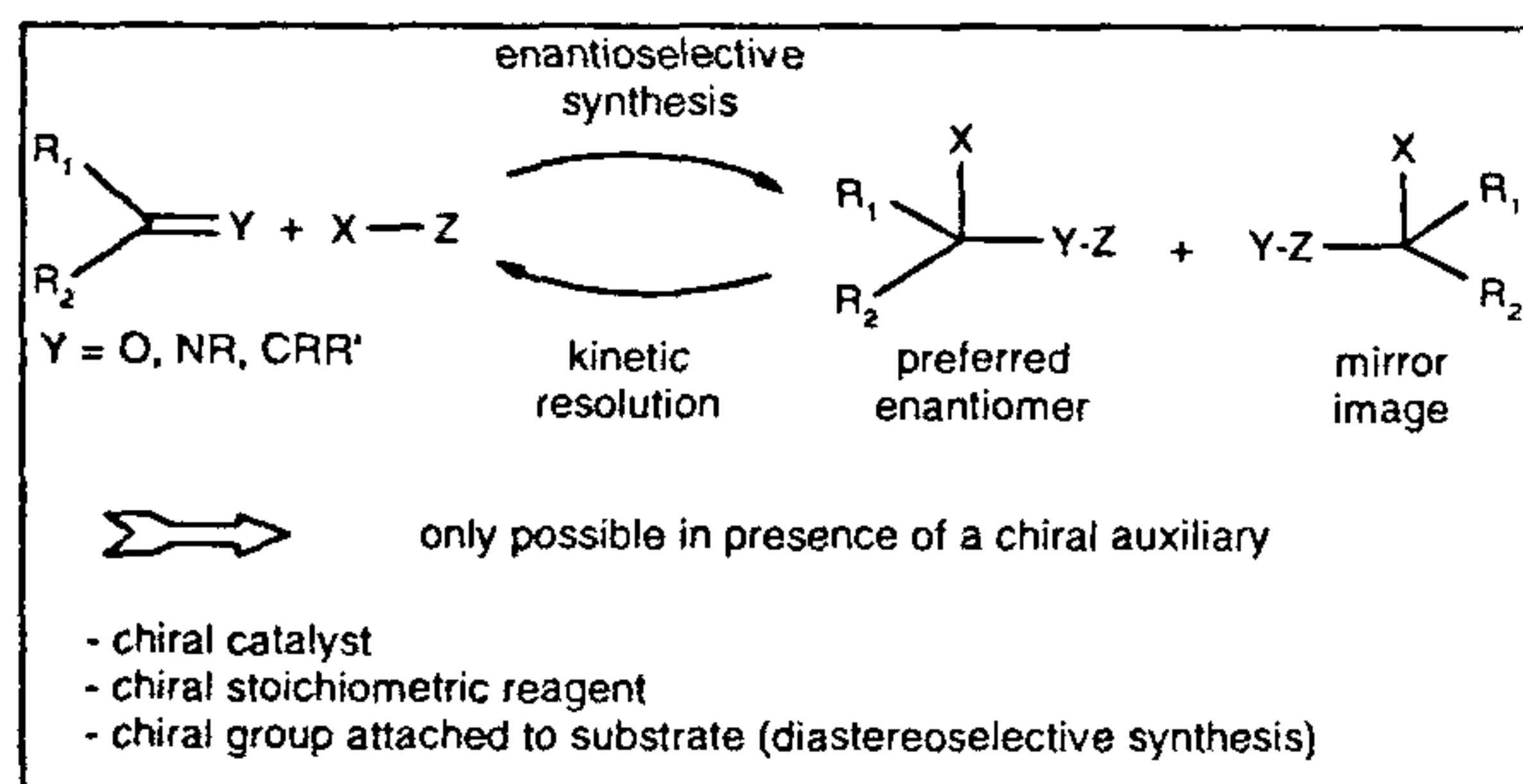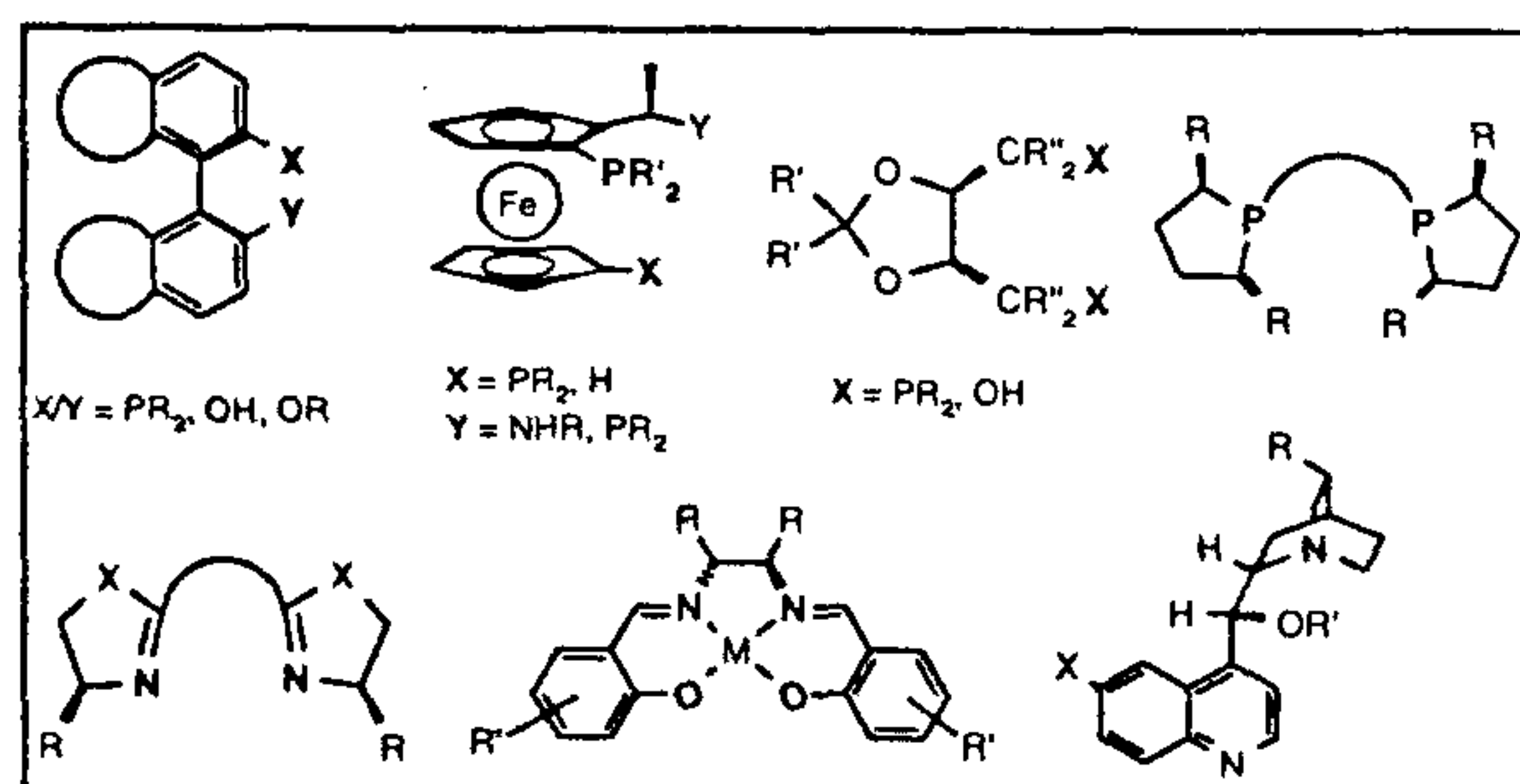
chiral auxiliary is used in sub-stoichiometric amounts only and multiplied via the catalytic cycle. Since a variety of ligand types are chiral, organometallic catalysts are extremely well suited for this task[5,6].

Arguably, the most important class of chiral ligands are tertiary phosphines, but amines and alcohols are also used. Effective chiral ligands are often bidentate, i.e. have two coordinating centres which are usually connected to a chiral organic backbone. Several chiral ligand types have proven to be effective for a variety of enantioselective transformations are depicted in Figure 4. Due to the high substrate specificity of most chiral catalysts, i.e. the fact that good enantioselectivity can be obtained only for a defined class of starting molecules and transformations, the right combination of metal and ligand has to be found for each individual reaction.

Even though enantioselective catalysis is still a young discipline, several enantioselective homogeneous catalytic processes are already applied on an industrial scale[7,8] and some of these will be described here.

The L-dopa process of Monsanto
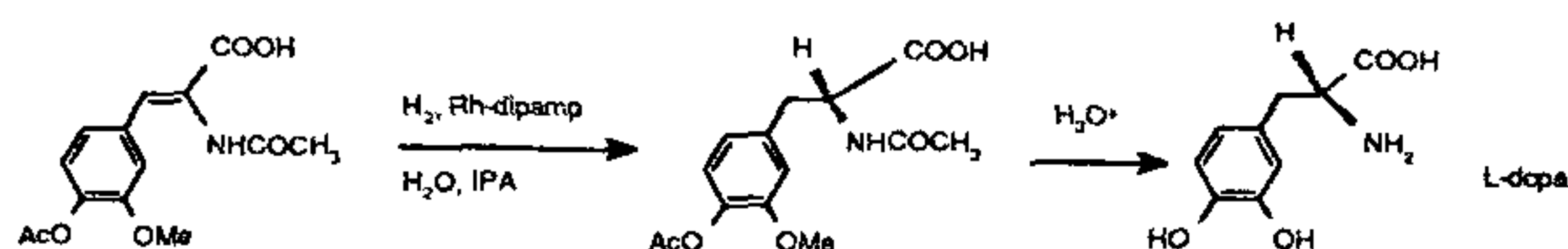
Scheme 1. L-dopa process of Monsanto.

According to Knowles[9], Monsanto has been producing L-dopa on a commercial scale for many years. The key step in this synthesis is the enantioselective hydrogenation of the enamide according to Scheme 1. Important aspects of the catalytic system are summarized in Table 2.
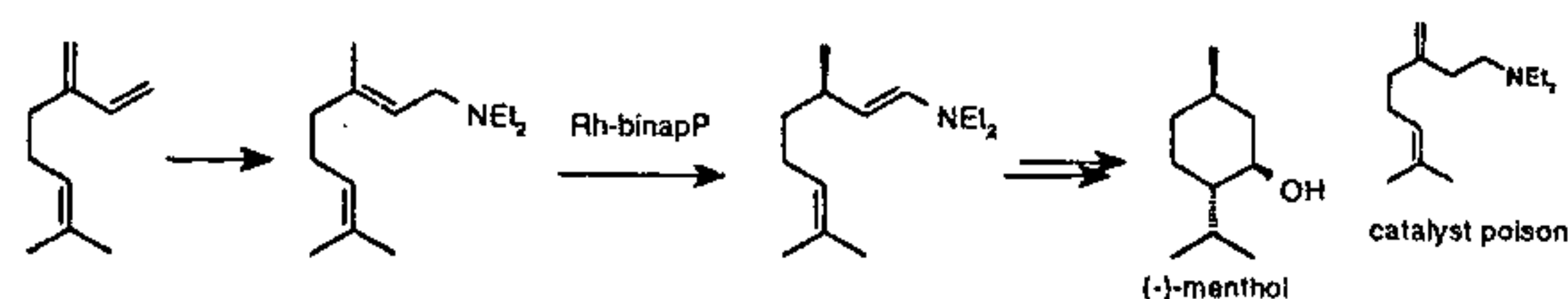
Table 2. L-dopa process, important aspects

Catalyst performance	95% ee, ton 10–20,000, tof 1000/h
Important features	Pure product (100% ee) crystallizes from the reaction mixture which allows the separation of both the catalyst and the undesired racemate.
Critical factors	Very pure starting material (no O_2, peroxides) is necessary for high performance. The free ligand racemizes slowly. Therefore, it is important to synthesize and isolate the corresponding Rh-complex.

Figure 3. Enantioselective synthesis and kinetic resolution.

Figure 4. Versatile chiral ligand types (coordinating atoms in bold face).

Comment. Ee-values of 95% are no longer exceptional for the hydrogenation of enamides (this was of course not the case at the time the process was developed). Therefore, the high turnover number and the possibility to separate the catalyst as well as the undesired enantiomer directly from the reaction solution are more important for the process performance. Strict control of the starting material quality is essential.

(-)-Menthol process of Takasago

As described by Akutagawa[10], Takasago produced 28,700 t (-)-menthol between 1983 and 1996 using only 250 kg of the chiral ligand BINAP. The key step in this menthol synthesis is the enantioselective isomerization of an allylic amine according to Scheme 2. Important aspects of the catalytic system are given in Table 3.


Scheme 2. Technical (-)-menthol synthesis of Takasago.

Table 3. (-)-Menthol process, important aspects

Catalyst performance	97.6% ee, ton 400,000, tof 1300/h
Important features	Active catalyst can be recovered and re-used after distillation. Ton increase from 8,000 > 80,000–400,000 (optimal work-up).
Critical factors	Starting material has to be highly purified and pretreated with NaAlH₂(OCH₂OCH₃)₂ (vitride). This increases the ton of the catalyst from 100 to 1000. Removal of a catalyst poison in the starting material shown on the left (only 0.07%!) increases ton from 1000 to 8000.

Comment. In this case, the right catalyst/metal combination was the most important parameter for a high enantioselectivity. However, it is clear that only a suitable quality of the starting material and the possibility to re-use the catalyst made the process commercially viable.

## Glycidol process of Arco (Sipsy)

The epoxidation of allylic alcohols using the cheap Ti/tartrate catalyst (Sharpless epoxidation, Scheme 3) has been developed to a versatile and efficient synthetic method that has been applied as the key step in multistep syntheses of bioactive compounds. The catalyst is effective for a variety of substituents at the C=C bond and tolerates most functional groups. A commercial process for both enantiomers of glycidol (R_1 or 2 = H) has been developed by Arco and is now in operation at Sipsy[11].
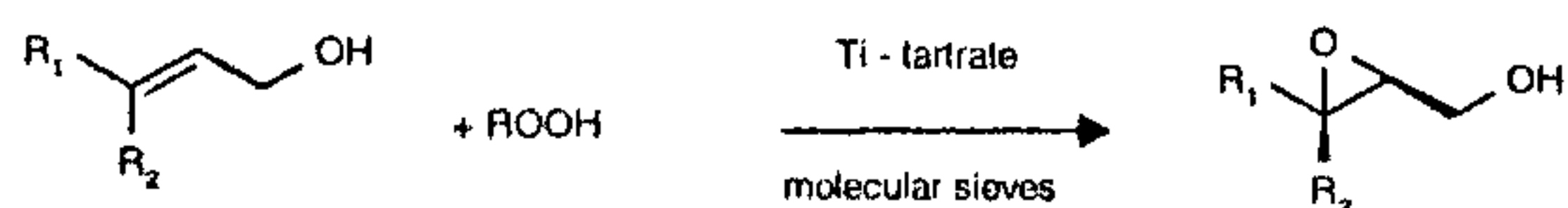

Scheme 3. Sharpless epoxidation of allylic alcohols.

Comment. Potential problems for the sharpless epoxidation are the stereoselective preparation of specific allylic alcohols, the handling of organic peroxides on a large

scale, sometimes the isolation and purification of the epoxy alcohols and the rather low catalytic activity of the Ti catalysts (ton usually around 20–40, tof in the range of 5–10 h⁻¹).

(S)-metolachlor process of Ciba-Geigy/Novartis
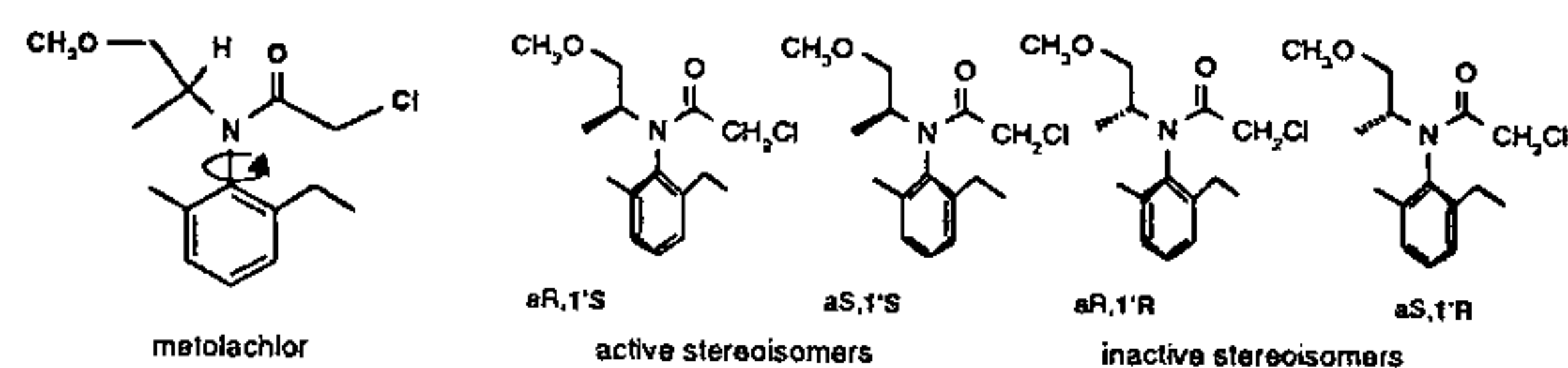
Scheme 4. Stereoisomers of metolachlor of Ciba-Geigy/Novartis.

Metolachlor is an active ingredient of Dual, one of the most important grass herbicides for use in maize and a number of other crops. It is an N-chloroacetylated, N-alkoxyalkylated ortho disubstituted aniline that has two chiral elements: a chiral axis (atropisomerism, due to hindered rotation around the C_{Ar}–N axis) and a stereogenic centre, leading to four stereoisomers of which the two 1'S-stereoisomers provide most of the biological activity (Scheme 4). Hydrogenation of the MEA imine (Scheme 5) is the key step in the production of the now commercially produced (S)-metolachlor. It took more than 10 years to develop the technical process but the result is one of the most active and productive enantioselective catalytic systems ever developed[12]. Important aspects of the catalytic system are given in Table 4.
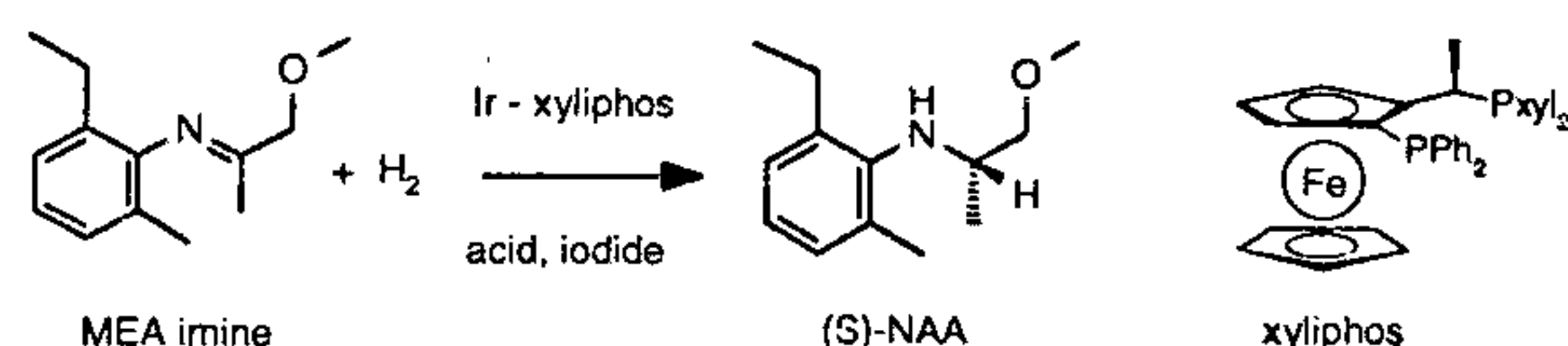
Scheme 5. MEA imine hydrogenation, structure of xyliphos ligand.

Table 4. (S)-Metolachlor production, important aspects

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Catalyst performance	80% ee, ton > 1,000,000, initial tof > 180,000/h
Important features	Extremely active and productive Ir–ferrocenyl diphosphine catalyst. Catalyst separation via distillation.
Critical factors	Basicity of ligand. Purity of starting material. Presence of acid and iodide is essential.

Comment. The very high ton and tof of the process and not so much the enantioselectivity were decisive for the success. The technical production of the MEA imine in the required quality and a large-scale synthesis for the ligand were important problems to be worked out. Scale up from the 50 ml screening autoclave via 6.3 l and 50 l stirred tanks and a 1000 l loop reactor to the final production autoclave was carried out without much problems. The catalyst and the process are very well behaved if all starting materials have the required quality.

C–C coupling reactions

The Heck reaction

Transition metal catalysed reactions open up new and important synthetic routes that have no analogies in the classical organic chemistry. A striking example is the Heck reaction, the Pd catalysed reaction of an olefin with an aryl derivative in presence of a base, where formally a vinylic hydrogen is replaced by an aryl group as shown in Scheme 6 (ref. 13, 14). The following sequence of elementary steps is generally accepted to explain the reaction: Oxidative addition of Ar–X to a Pd⁰ species; coordination and insertion of the C=C group; β-elimination and dissociation of Ar–C=C and reductive elimination of HX to return to the Pd⁰ species. The method is highly versatile because a wide variety of aryl as well as olefin derivatives can be used and also because most functional groups are tolerated.
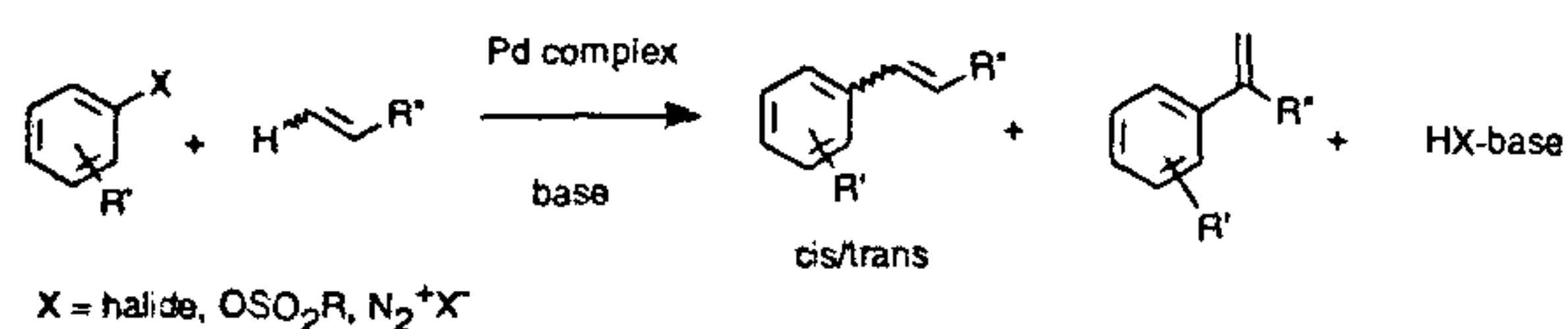

Scheme 6. Heck reaction, principle and possible isomers.

Preferred catalysts are palladium complexes, often used together with phosphine ligands. With the more reactive aryl iodides and bromides, no phosphine ligands are necessary and also heterogeneous catalysts like palladium on charcoal are effective. However, there is some controversy as to whether metallic or partially dissolved palladium is the active catalyst.

The reactivity of the olefinic starting material decreases with the number of substituents on the double bond. Ethylene is therefore the most reactive one but selectivity can be a problem due to further reaction. Monosubstituted alkenes react smoothly, whereas higher substituted olefins often give unsatisfactory yields. Depending on the substituents of a monosubstituted olefin, the aryl moiety is attached either to the terminal or the internal carbon and the resulting stereochemistry of the double bond can be either E or Z. As a consequence, many olefins give product mixtures which are sometimes difficult to separate. Suitable substrates are in general olefins bearing electron withdrawing groups such as acrylates or acrylonitriles. These olefins are mainly attached at the terminal carbon giving linear products. Aryl bromides and aryl iodides, especially bearing electron- withdrawing substituents are the preferred substrates. They can easily be activated and palladium loadings can be as low as 0.0001 mol%. However, aryl bromides and aryl iodides are relatively expensive, and the heavy halide atom is lost in the process or must be recycled. Alternatives are diazonium compounds

and especially the generally cheap aryl chlorides, which unfortunately have a much lower reactivity and require higher Pd loadings. In the last few years, new catalyst systems with very basic and bulky phosphines have been developed to make the use of aryl chlorides technically feasible[15].

Until now, several production processes have been developed using Heck methodology. The Dead Sea Company produces octyl-4-methoxycinnamate, the most common UV-B sunscreen, via the Heck reaction depicted in Scheme 7 (ref. 15). In the first step, anisole is brominated in the 4-position with 97% selectivity. Then the Heck reaction with octyl acrylate is carried out using a heterogeneous Pd on carbon catalyst that can easily be separated from the product. However, the catalyst is not very active and the reaction has to be carried out at 180°C. Another important factor for the commercial success of this process is the re-oxidation of NaBr that is recycled to bromine.
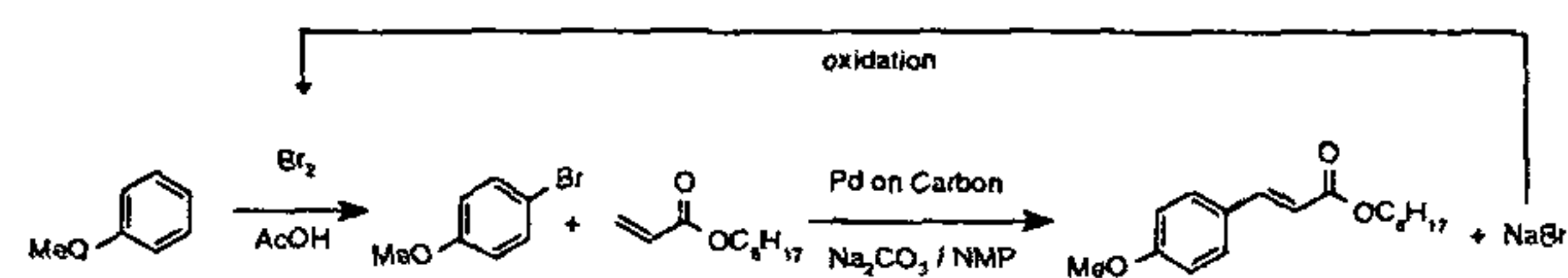
Scheme 7. Process for octyl-4-methoxycinnamate.

Albemarle produces Naproxen, a generic analgesic, via the reaction sequence bromination – Heck reaction – carbonylation (see Scheme 8)[17]. The process is commercially attractive because methoxy naphthalene is a relatively cheap starting material, bromine is again recycled and the carbonylation reaction proceeds with high selectivity.
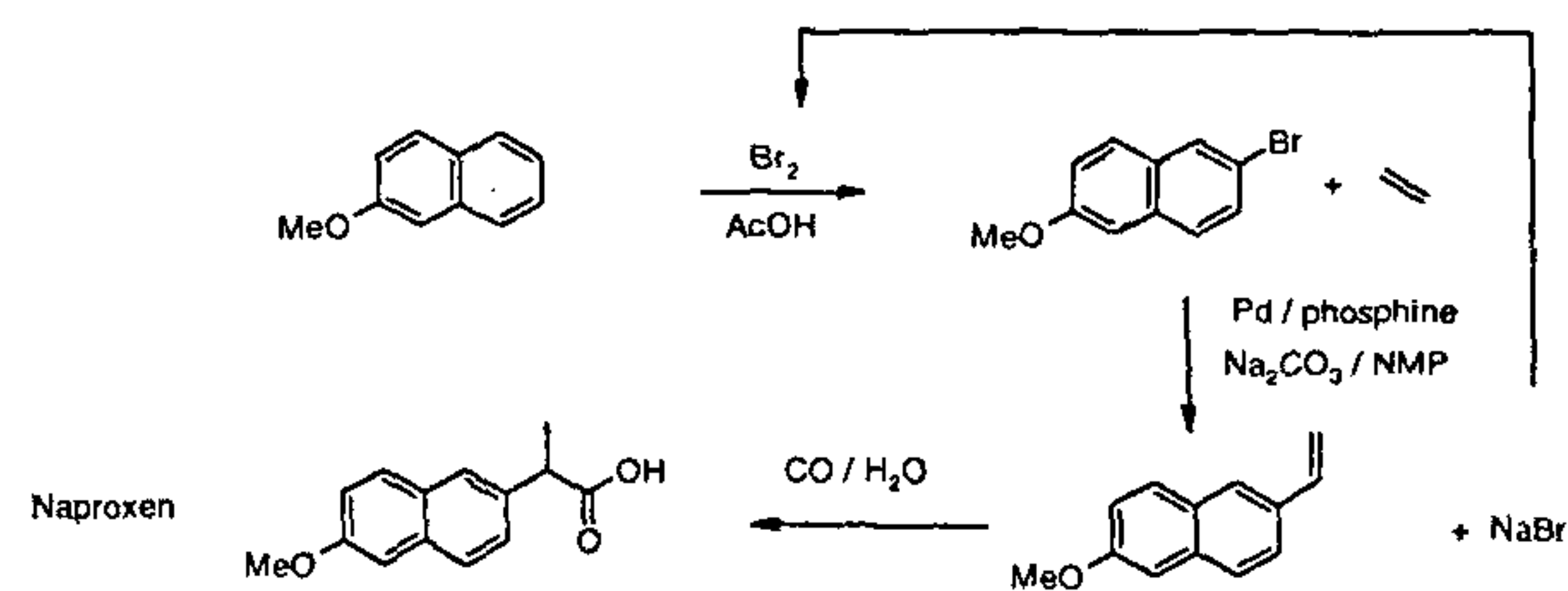

Scheme 8. Naproxen process of Albemarle.

During the development of the Heck reaction various problems had to be solved. Obviously, regioselectivity is no problem with ethylene. However, the vinylnaphthalene produced is a rather reactive olefin. It polymerizes easily and also can undergo a second Heck reaction to the stilbene derivative. To avoid polymerization, the reaction is run at unusually low temperatures (80°C) using a proprietary, highly active homogeneous palladium phosphine catalyst. The formation of stilbene is suppressed by using a large excess of ethylene by running the reaction at high ethylene pressures.

The third example concerns sodium 2-(3,3,3,-trifluoro-propyl)-benzenesulfonate, a key intermediate for Novartis' sulfonylurea herbicide Prosulfuron. Because all attempts failed to find a classical synthetic method such as a Friedel–Crafts alkylation, a technically feasible production process had to be developed based on a methodology until that was only used on a laboratory scale[17].
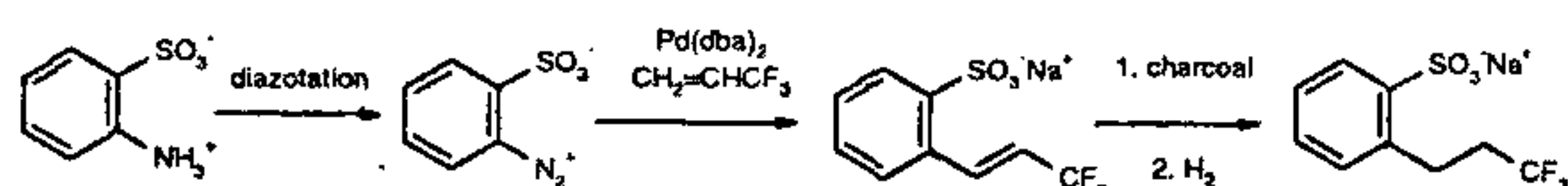
Scheme 9. One-pot synthesis of a Prosulfuron intermediate (Ciba-Geigy/Novartis).

A so-called 'one-pot' process was developed combining the diazotation of 2-aminobenzenesulfonic acid, a Heck-type reaction and a hydrogenation step without isolation of the diazonium or olefin intermediates (Scheme 9). The hydrogenation was carried out with an *in situ* formed Pd on carbon catalyst (by simply adding active carbon to the reaction mixture). The required sodium trifluoro-propyl-benzenesulfonate was obtained in 93% yield, i.e. an average of 98% per step. Moreover, only 2 kg wastes/kg product were produced during the three consecutive synthetic steps. This example illustrates a trend in fine chemical production technology, namely to combine several steps in one pot in order to get efficient processes. It also shows an elegant way to separate a homogeneous Pd catalyst by adsorption on active carbon followed by filtration and Pd recovery by the catalyst manufacturer.

These three examples serve to show that the Heck reaction is a valuable technology for the production of fine chemicals, and that technical problems such as catalyst separation or catalyst activity may be solved. So far aryl bromides are the most versatile starting materials but because of their relatively high price, an industrial process seems only to be competitive when bromination and bromine recycling is part of the process. Therefore, it is not surprising that the two companies mentioned above are important producers of bromine, and have the facilities to recycle bromine.

Cross coupling reactions

The palladium and nickel catalysed cross coupling reactions of organic halides with organometallic complexes of have been developed to a point where they are powerful tools for the synthetic chemist; some of these are now even established as so-called 'name reactions'[19]. Especially the Suzuki[20] and Stille[21] coupling reactions (see Scheme 10) have attracted much attention, mainly because the arylboronic acids and the aryl tin compounds are compatible with nearly all functional groups. In the presence of a palladium catalyst, aryl iodides and aryl bro-

mides can be coupled to form biphenyl groups under very mild conditions. For the less reactive aryl chlorides protocols were developed using nickel catalysts. Because most of these reactions have still low catalyst activities and turnover numbers, they are mainly used for small scale laboratory syntheses, but some industrial processes have been described in recent years.
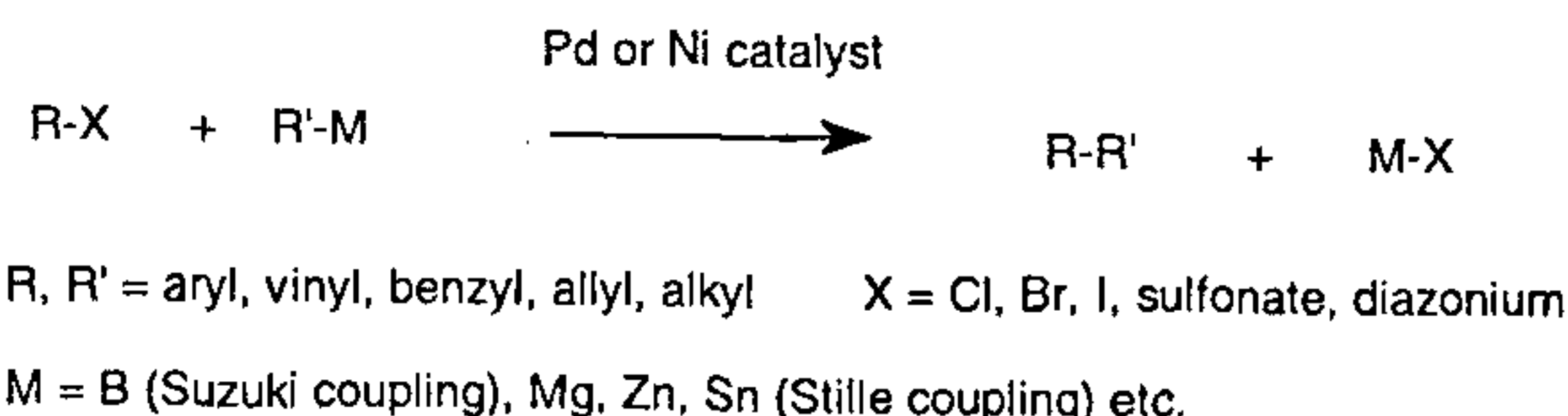
Scheme 10. Different types of cross coupling reactions.

4'-methyl-2-cyano-biphenyl is a key intermediate for the production of several angiotensin II receptor antagonists against high blood pressure such as Valsartan (Novartis) or Losartan (DuPont). Clariant produces 4'-methyl-2-cyano-biphenyl using the Suzuki coupling depicted in Scheme 11 (ref. 22). In general, aryl chlorides are not reactive enough for palladium catalysts. However, in this special case the aryl-chlorine bond is highly activated by a strongly electron-withdrawing nitrile group in 2-position. Coupling between the tolylboronic acid and the 2-chloro-benzonitrile is carried out in a two-phase process. A water soluble, sulfonated phosphine is used to keep the Pd–phosphine complex in the aqueous phase and the organic product can be separated from the catalyst by a simple phase separation.
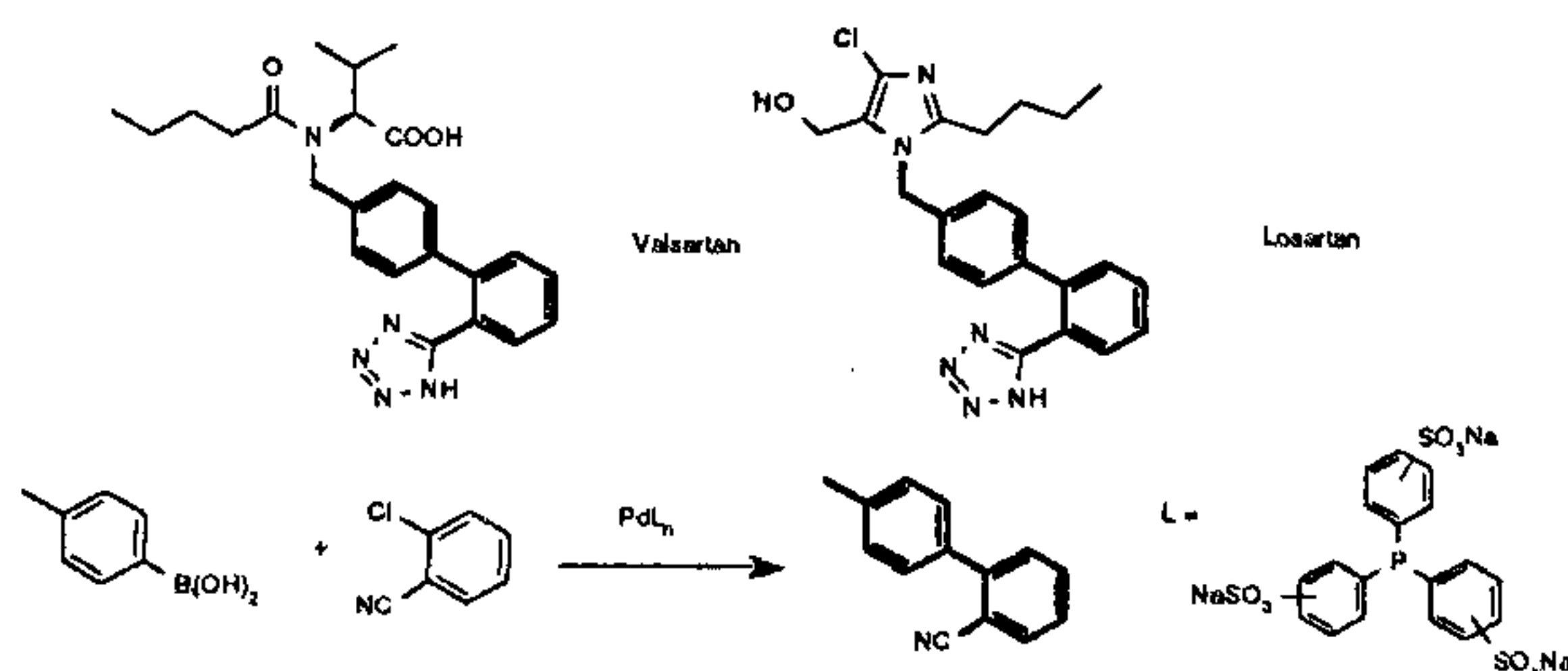
Scheme 11. Suzuki coupling for the production of 4'-methyl-2-cyano-biphenyl (Clariant).

Terbinafine, an antimycotic agent, is produced by Novartis via the Pd catalysed reaction of a vinyl chloride with a terminal acetylene (Sonogashira coupling, Scheme 12)[23]. In the presence of 0.05 mol% of the stable, commercially available bis-(triphenylphosphine)–PdCl₂ complex and with 5% CuI as co-catalyst, the yield is > 95%. The reactive intermediate is probably a copper acetylide complex which reacts with the palladium vinyl complex. The stereochemistry at the double bond is completely preserved, a feature common to these reactions.
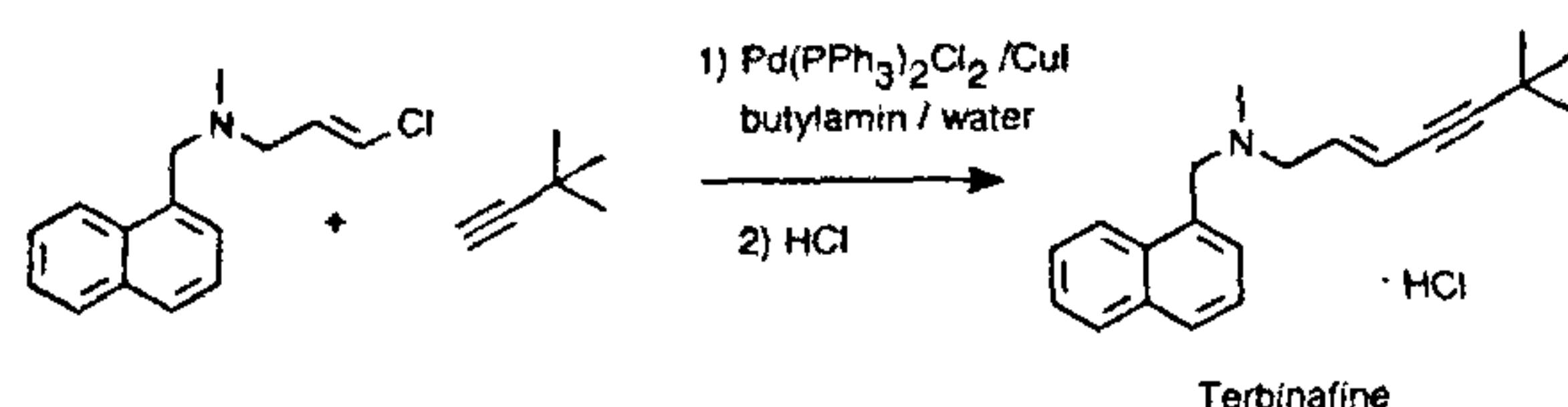
Scheme 12. Synthesis of terbinafine (Sandoz/Novartis).

In recent years the scope of the palladium catalysed coupling reactions of aryl halides has been extended to heteroatom nucleophiles like nitrogen, phosphorous, sulphur or oxygen compounds to give aromatic amines, phosphines, thioethers or ethers which are not easy to synthesize using conventional methods[24]. It can be expected that additional novel and useful Pd and Ni catalysed processes will be developed in the near future.

Carbonylation reactions

A carbonylation reaction (sometimes also called carboxylation) is defined here as a reaction that uses CO as a C_1 building block (see Scheme 13). These reactions are catalysed by transition metal catalysts such as Rh, Pd, Co or Ir complexes. Carbonylation chemistry has been used for the synthesis of bulk chemicals for over 50 years and several large processes are presently in operation[25]. In the fine chemicals industry there are as yet few applications since many of the products such as ketones or carboxylic acid derivatives can be prepared easily using classical organic methods. Another hurdle for the fine chemical industry is the need to build up a CO infrastructure including pressure vessels and also safety issues can be a problem. However, since most carbonylation reactions have a good atom economy, i.e. most reagent atoms are transferred to the product, interest in their application has increased for ecological reasons. In this chapter, two very large scale as well as some smaller applications in the fine chemicals industry will be described.
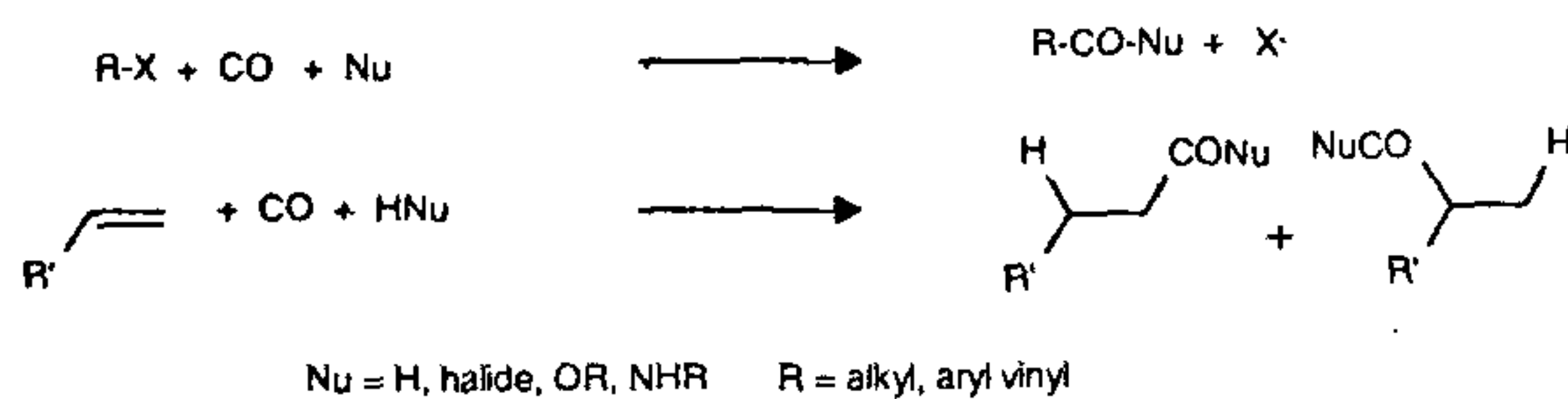

Scheme 13. Various types of carbonylation reactions.

Acetic acid process (Monsanto)

A very impressive example for a large-scale carbonylation process is the production of acetic acid from methanol. BASF developed a Co catalysed process which dominated the market until 1978 that needed very high temperatures (up to 210°C) and pressures (up to 700 bar). This process

was slowly replaced by a Rh catalysed version developed by Monsanto[26] and now, a third generation process is introduced by BP using Ir complexes instead of Rh. In the Monsanto process methanol is converted to acetic acid at only 30–40 bar of CO using 0.1 mol% of a rhodium catalyst and an iodide promoter (MeI, HI, I_2) at a temperature of 180°C. The reaction has been studied in great detail and its mechanism is well-established (see Scheme 14). The catalyst precursor is $RhCl_3 \cdot 3H_2O$ that under reaction conditions is rapidly converted to the active species $[Rh(CO)_2I_2]^-$. The major role of the iodide promoter is the conversion of methanol to the more electrophilic methyl iodide (nucleophile, cycle II), but it also acts as a ligand (cycle I), a leaving group (cycle I) and a weak Broensted base (cycle II). It is noteworthy, that only iodine can meet all these requirements. The reaction is carried out in a continuous back-mixed reactor and the acetic acid is separated from the catalyst solution and forwarded with dissolved gases to the distillation section. Since the rhodium compounds are relatively nonvolatile, they stay in the reactor loop for years and can be re-used many times.
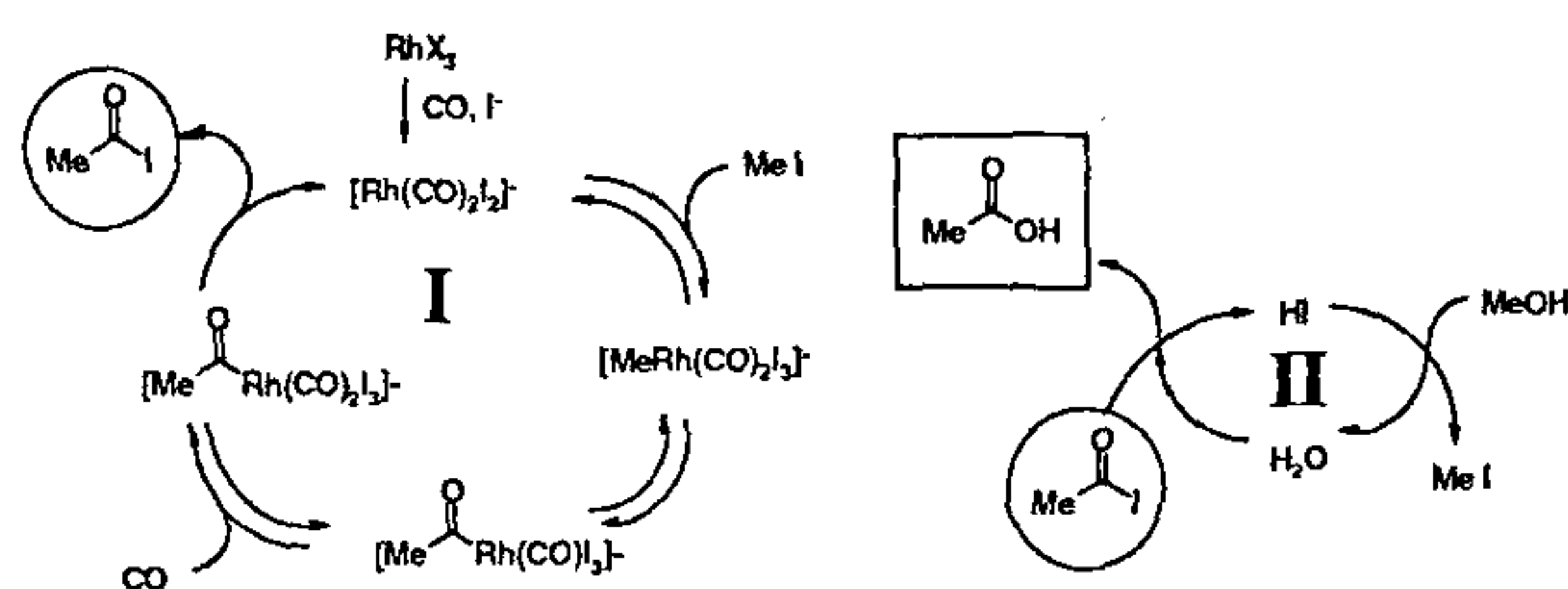
Scheme 14. Proposed mechanism of the Monsanto acetic acid process[26].

Pd catalysed carbonylation of aromatic halides

The related, Pd catalysed reaction of aryl halides with CO in presence of a nucleophile (see Scheme 15) has a broad scope and offers interesting opportunities to the organic chemist[13]. For aromatic and heteroaromatic carboxylic acid derivatives chemical yields are generally high but catalyst activity and turnover numbers are often a problem. The reductive carbonylation to the corresponding aldehyde either in presence of hydrogen gas or hydride donors (Nu = H⁻) is a very useful transformation but chemical yields as well as catalyst performance are yet not sufficient for most technical applications. This is also
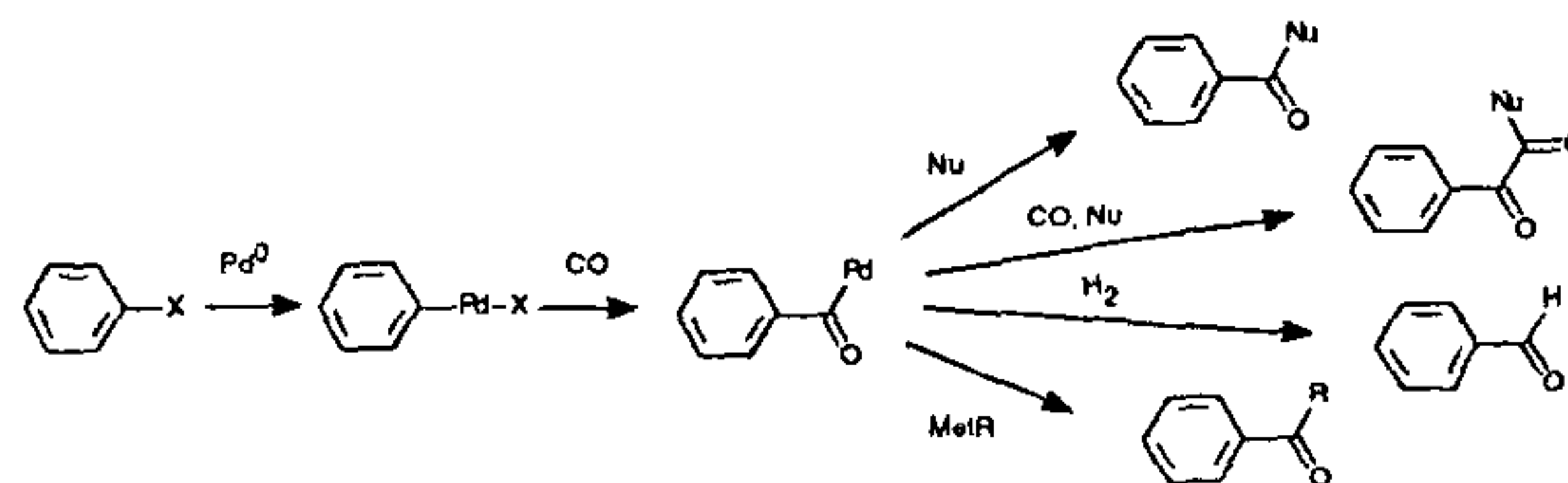
Scheme 15. Pd catalysed carbonylation of aryl halides and related starting materials.

the case for the synthesis of ketones using CO and metal alkyl compounds and for the double carbonylation to give α-keto acid derivatives.

Hydroformylation of alkenes

Hydroformylation, i.e. the Rh or Co catalysed addition of CO and H_2 to an alkene to produce the corresponding aldehyde(s) is one of the oldest catalytic reactions[25]. The problem of regioselectivity and sometimes also catalyst activity and the necessary pressure can be a major hurdle for its application. In the bulk chemical industry it has been practised commercially since the early 1940s for the production of short and long chain aldehydes and alcohols. As illustration we give a short description of two competing versions of the Rh catalysed hydroformylation of propylene to form butyraldehyde developed concurrently by Union Carbide/Davy Powergas and Johnson Matthey (UCC)[27] and Ruhrchemie/Rhône–Poulenc (RRP)[28], respectively. The UCC version uses the Wilkinson complex $(Rh(PPh_3)_3Cl)$ catalyst at 15–18 bar and 90–95°C. The aldehydes are removed from the catalyst solution by continuous distillation; the catalyst stays in solution (high boiling aldehyde condensation products) and can be used for up to one year. The over-all equipment is very complex in order to get an optimal performance. The RRP process is based on the idea to use a water soluble rhodium complex as catalysts and work in a two-phase mode (water/aldehyde). This process is carried out continuously in a stirred tank reactor at 40–60 bar and 110–130°C. The phases are separated in a phase separator and the organic phase is then distilled in a strip column (the so-called n/i column). The ratio of linear/branched product (n/i) is about 8 for the UCC and 19 for the RRP process. While the catalyst of the classical UCC process is cheaper than the sulfonated variation, a significant advantage of the RRP process lies in the better over-all selectivity because the distillation occurs in absence of the catalyst. But it seems that the economics of the two processes are relatively close.

As pointed out earlier, addition reactions of CO and HNu to a C=C bond are less common in the fine chemicals industry. An example was already given in Scheme 8 for the synthesis of Naproxen, where a Pd catalysed hydrocarboxylation leads directly from the vinylic intermediate to the end product. Other application of the hydroformylation methodology are two alternative approaches for the synthesis of a vitamin A intermediate developed by Hoffmann-La Roche[29] and BASF[30], respectively (see Scheme 16). In the BASF process, the internal is first isomerized to the terminal olefin. This is more reactive but both the undesired linear as well as the desired branched aldehyde are formed. The target intermediate is obtained via selective elimination of acetic acid from the branched product; the linear aldehyde is recovered and
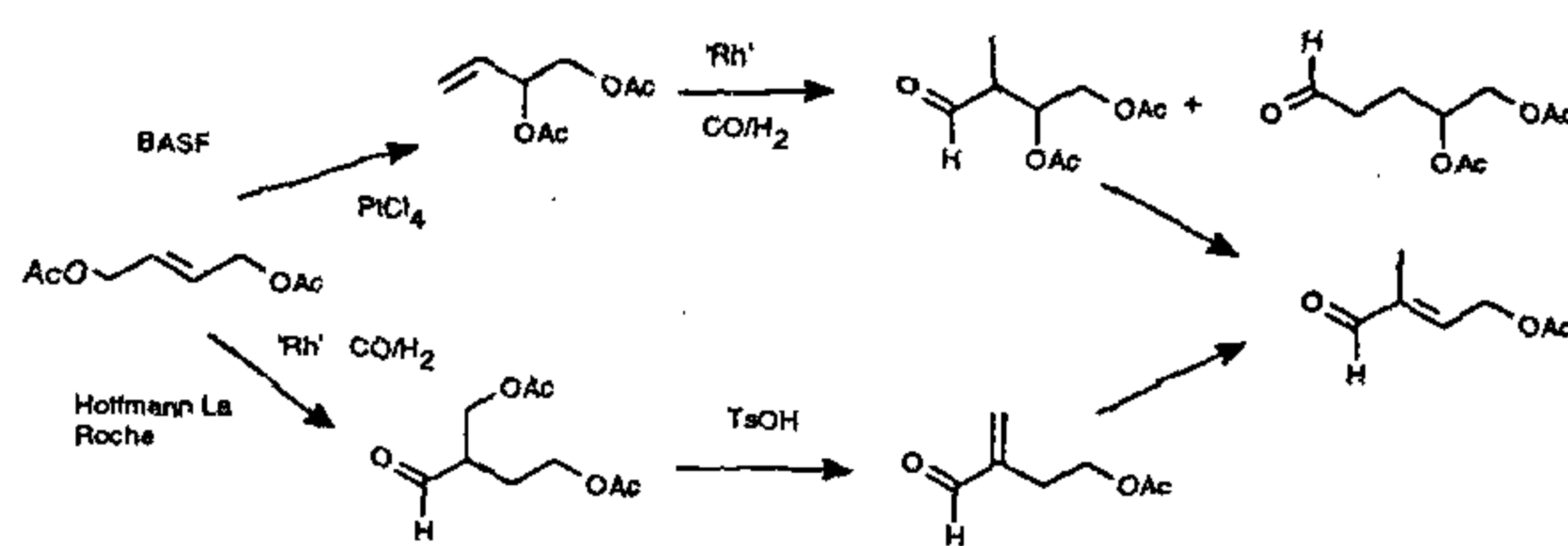
Scheme 16. Two alternative approaches for the synthesis of a vitamin A intermediate.

converted to 1,2,5-pentanetriol to be used in synthetic lubricants[30]. Roche has developed a catalyst to hydroformylate the internal olefin. As a consequence, no regioselectivity problems occur and the process is very economical.

Outlook

In our opinion, the prospects for the application of homogeneous catalysts by organometallic complexes look very good for some of the following reasons: More and more organic chemists have a good training in this topic (and chemists only apply reactions that they know well!). Academic research is very productive and we expect that additional useful catalytic transformations will be found that can be developed for industrial use. In order to stay competitive and to fulfill modern ecological requirements, companies will choose more catalytic routes since these are sometimes shorter or lead to cheaper processes.

In the fine chemicals industry, we would expect development in the following directions because existing catalysts are either already mature or will be soon ready for industrial use. The applications of chiral metal complexes for asymmetric hydrogenation, epoxidation, dihydroxylation, epoxide ring opening (also kinetic resolution) and cyclopropanation reactions; C–C bond forming reactions such as the Suzuki coupling or the Heck reaction, as well as carbonylation reactions that lead to unusually substituted aromatic compounds. Another reaction of current interest that soon might be technically applicable is ring closing metathesis to make a variety of small and medium sized ring systems.

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MEETINGS/SYMPOSIA/SEMINARS

International Conference on Trends in Mechanical Alloying: Science, Technology and Applications

Date: 21–23 February 2001
Place: Jaipur, India

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International Conference on Remote Sensing and GIS/GPS

Date: 1–4 December 2000
Place: Hyderabad, India

Themes include: *Focal Theme*: Spatial information technology for disaster management. All aspects of forecast, warning, management covering pre and post-disaster issues concerned with earth, environment and people. *GIS/GPS*: Applications, Four dimensional GIS, Digital elevation and terrain modelling, Automated mapping – facilities management, Object-oriented GIS and its applications. *Education*: Training and Internet/Web. Education and training modules. Human resource development, Curriculum development, Textbooks, Global scenario, GIS and maps and web-based GIS applications. *Physics and thematic mapping*: Spectral signatures, Remote sensing application for water resources, soils agriculture, irrigation and command area development, Land use, Geo-sciences and urban and regional planning. *Biosphere monitoring*: Hydrology, forestry, integrated surveys, ecology, environmental impact assessment, Green house gases and atmospheric pollution. *Marine Environment*: Coastal zone management, Ocean colour, SAR applications, Marine pollution and marine GIS. *Photogrammetry*: Soft copy/ digital photogrammetry, cartography, cadastral surveying, topographical surveying, total station and GPS applications and map updating. *Digital image processing*: Image analysis and classification, fusion, hyperspectral image processing, mathematical morphology, neural networks, Atmospheric corrections and change detection. *Satellite missions and very high resolution data*: Thematic mapping on very large scale, collateral data requirements and integration, case studies of thematic applications and satellite missions. *Global Issues*: Data bases, design, maintenance and updating, formats, spatial and temporal intervals, security, accuracy and international/national protocols and meta data for every one.

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