

# Applications of Rhodium-Catalyzed Hydroformylation in the Pharmaceutical, Agrochemical, and Fragrance Industries

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**Abstract** This review summarizes the known commercial applications of rhodium-catalyzed olefin hydroformylation to fine chemical synthesis. Two manufacturing processes for Vitamin A utilize hydroformylation. Additional, recent examples of hydroformylation on multikilogram scale for synthesis of pharmaceutical building blocks have also been reported. Hydroformylation appears to be widely used in the fragrance industry, where aldehydes are ubiquitous. Numerous fragrance ingredients are commercially prepared by hydroformylation. There are no reports of agrochemical manufacturing processes which employ hydroformylation. In addition to commercial applications, examples of pharmaceutical, fragrance, and agrochemical products which have been prepared on small scale using hydroformylation are given. Hydroformylation appears to be well suited to fine chemical synthesis, and applications should increase as process chemists become more aware of its potential.

**Keywords** Carbonylation · Hydroformylation · Rhodium · Syngas

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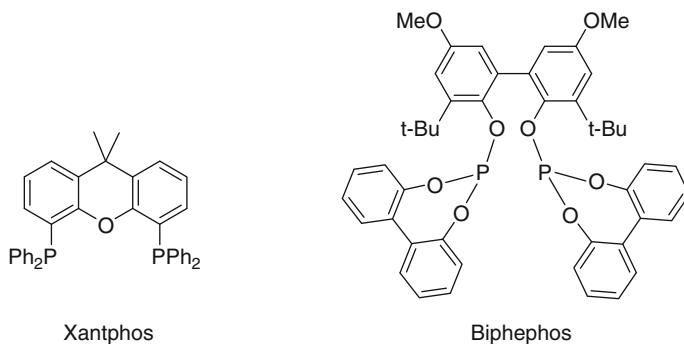
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## 1 Introduction

Rhodium-catalyzed olefin hydroformylation is widely used for the manufacture of a variety of commodity chemicals [1]. Propylene and butene hydroformylation leads to so-called Oxo alcohols which are transformed into industrially important solvents and coating materials. Higher olefins are converted via hydroformylation into plasticizer and detergent alcohols, and hydroformylation of allyl alcohol is an important route to 1,4-butanediol and its derivatives. Despite its widespread use in the manufacture of cheap, commodity chemicals, commercial applications of rhodium-catalyzed hydroformylation in the pharmaceutical and fine chemical industries are rare. At first glance, one would expect quite the opposite; it should be more practical to use expensive rhodium catalysts to produce complex targets with higher profit margins. However, separation of the aldehyde product from the expensive Rh catalyst has historically presented a challenge, and, as a result, most commercial applications involve hydroformylation of lower olefins where the aldehyde product can be separated by distillation. A variety of separation schemes have been developed, e.g., biphasic systems, immobilized catalysts, etc., which should facilitate the application of Rh-catalyzed hydroformylation to more complex, nonvolatile products. Unfortunately, hydroformylation is not in the typical synthetic organic chemist's repertoire and is underutilized as a route to aldehyde intermediates by process chemists outside of the commodity chemicals industry. Realistically, for more complex targets, any synthetic method must compete with a variety of other synthetic disconnections on factors such as cost, complexity, and waste treatment. A significant advantage of hydroformylation is perfect atom economy, and ligands developed within the past 20 years offer excellent regioselectivity [2–4], chemoselectivity, and functional group tolerance. For example, xantphos and biphephos ligands lead to high selectivity for linear aldehydes from terminal alkenes (Fig. 1). Both of these ligands are now commercially available for screening purposes and are commonly used in fine chemical applications.

This review attempts to highlight the application of rhodium-catalyzed hydroformylation in the manufacture of pharmaceuticals, agrochemicals, and fragrances.



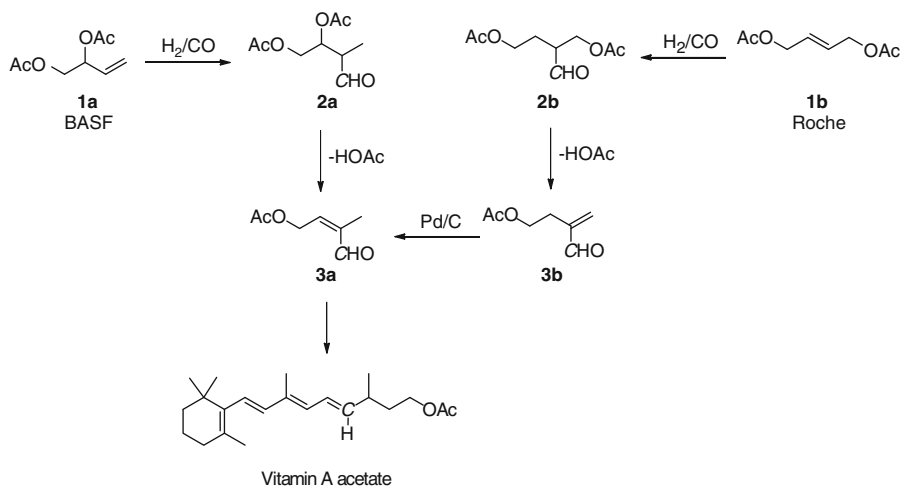
**Fig. 1** The most commonly used ligands for highly linear regioselective hydroformylation

A thorough review of the scientific and patent literature was performed to identify examples of hydroformylation of complex substrates which might form the basis of commercial processes. Since industrial companies typically do not disclose their actual manufacturing process, some speculation is necessary. Often the scale of the reactions is indicative of the level of commercial interest in a given hydroformylation reaction. Additionally, reports of the use of hydroformylation in an alternative synthesis of a launched pharmaceutical or agrochemical are also suggestive of potential commercial interest.

## 2 Pharmaceuticals

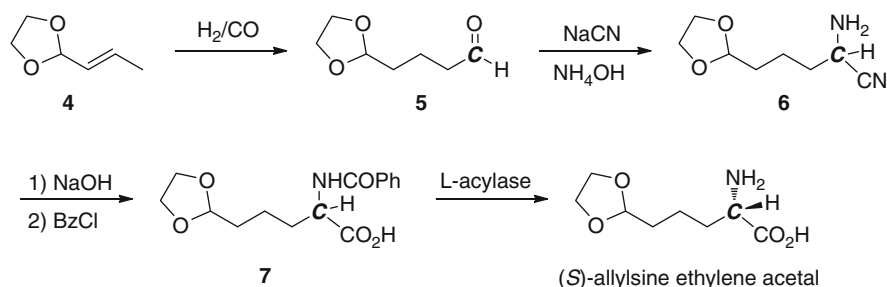
Two manufacturing routes for Vitamin A utilize rhodium-catalyzed hydroformylation for the synthesis of an aldehyde intermediate (Fig. 2) [5]. The process developed at BASF involves hydroformylation of 1,2-diacetoxy-3-butene (Fig. 2, **1a**) to give the branched aldehyde (Fig. 2, **2a**) [6]. Elimination of acetic acid gives the  $\alpha,\beta$ -unsaturated aldehyde (Fig. 2, **3a**) which leads to Vitamin A acetate by Wittig reaction. An analogous process was developed by Roche starting from 1,4-diacetoxy-2-butene (Fig. 2, **1b**). Hydroformylation gives aldehyde **2b**, which eliminates acetic acid to give **3b** which is then isomerized to **3a**.

The only other application of hydroformylation applied to the synthesis of a pharmaceutical intermediate on a commercial scale has recently been reported. The synthesis of (*S*)-allysine ethylene acetal, an intermediate in the manufacture of angiotensin I-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitors, was reported by researchers at Dr. Reddy's and Chirotech using a combination of

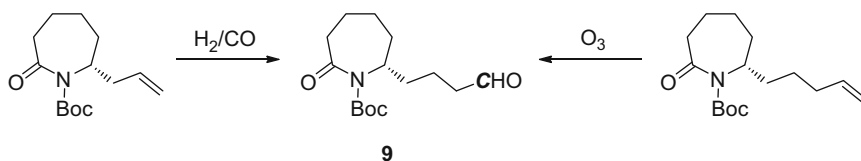


**Fig. 2** BASF and Roche processes for manufacture of vitamin A using rhodium-catalyzed hydroformylation. Carbon atom derived from carbon monoxide is highlighted in *bold*

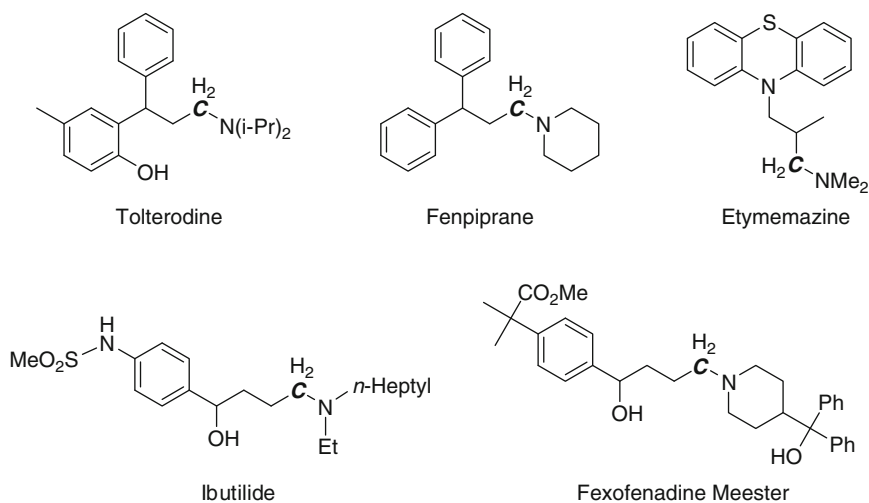
hydroformylation and enzymatic catalysis (Fig. 3) [7]. Crotonaldehyde ethylene acetal (Figs. 3 and 4) was hydroformylated to the linear aldehyde (Figs. 3 and 5) using the Rh-biphephos catalyst. Tandem isomerization/hydroformylation of **4** was performed with a 4,000:1 molar substrate/catalyst ratio at 80°C under 3 bar of 1:1 H<sub>2</sub>/CO. The desired regioisomer was formed with a linear/branched ratio of 15:1.



**Fig. 3** Synthesis of (*S*)-allysine ethylene acetal by rhodium-catalyzed asymmetric hydroformylation



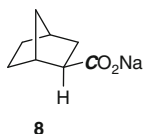
**Fig. 4** Comparison emphasizing the synthetic equivalence of linear-selective hydroformylation and ozonolysis



**Fig. 5** Examples of pharmaceutical targets which have been prepared by hydroformylation-reductive amination

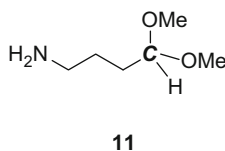
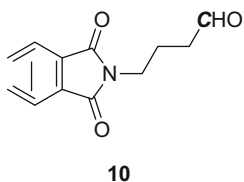
The regioisomeric mixture of aldehydes was isolated by organic-aqueous extraction. The aldehyde was extracted into the aqueous phase, which allowed separation of the catalyst and ligand into the organic phase. The hydroformylation reaction was performed in multiple batches using a 300-L pressure reactor. Aldehyde **5** was converted via Strecker reaction in a 10,000-L reactor to produce multiton quantities of **6**. Aminonitrile (**6**) was hydrolyzed and then benzoylated to give racemic **7** which was converted to (*S*)-allysine ethylene acetal by enzymatic resolution. The enzyme selectively hydrolyzed only the (*S*)-enantiomer of the linear product, facilitating easy separation from both the undesired enantiomer and branched regioisomer.

Workers at Pfizer have recently described hydroformylation on kilo-lab scale to prepare a pharmaceutical building block [8]. Hydroformylation of norbornylene (8.0 kg) using 0.15 mol% Rh(CO)<sub>2</sub>(acac) with dppf (1,1'-bis(diphenylphosphino)ferrocene) (45 psi H<sub>2</sub>/CO, 35°C, *t*-BuOH) gave exclusively the *exo*-aldehyde. Oxidation with NaClO<sub>2</sub> and TEMPO (2 mol%) was performed directly on the *t*-BuOH solution from the hydroformylation reaction to give 2-*exo*-norbornyl carboxylic acid which was isolated as the sodium salt, **8**, in 80% overall yield.

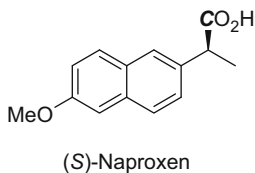


Several pharmaceutically relevant examples are found in the patent literature where hydroformylation reactions are performed on significant scale (>100 g substrate). For example, researchers at Pharmacia (now Pfizer) reported the hydroformylation of *N*-Boc-(*S*)-7-allylcaprolactam on 250-g scale using Rh-biphephos to give aldehyde **9** (Fig. 4) with 96% linear selectivity [9]. Ozonolysis of the 7-pentenylcaprolactam derivative was used for smaller scale preparation of **9**. Hydroformylation is a safer process equivalent to ozonolysis which is more amenable to scale-up.

Hydroformylation of *N*-allyl phthalimide on 200-g scale was described in a recent patent by Dow [10]. Using the Rh-biphephos catalyst, the desired linear aldehyde (**10**) was produced in 11.5:1 linear/branched ratio. Acetal protection of the aldehyde and cleavage of the phthalimide gave the protected amino aldehyde (**11**), useful as a pharmaceutical intermediate.

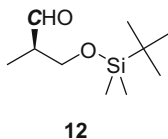


Vinyl arenes are the most studied substrates for application of asymmetric hydroformylation to pharmaceutical synthesis. The resulting, branched aldehyde regioisomers can be oxidized to  $\alpha$ -aryl propionic acids, which constitute a class of nonsteroidal anti-inflammatory drugs (NSAIDs). Of these, (*S*)-Naproxen, is sold as a single enantiomer. A rhodium-catalyzed hydroformylation route to racemic Naproxen was first reported by Brown using sugar-derived phosphines [11]. In the late 1980s, Parrinello and Stille reported the first asymmetric hydroformylation synthesis of (*S*)-Naproxen using a Pt-bisphosphine catalyst [12]. Significant work was done subsequently in both academic and industrial labs



which led to efficient asymmetric hydroformylation catalysts with both high enantioselectivity and regioselectivity for vinyl arene hydroformylation. However, the efficient process economics of the resolution used in the manufacture of (*S*)-Naproxen, combined with the relatively high cost of the olefinic substrate, makes asymmetric hydroformylation economically unviable as a route to this particular drug [13]. During the 1990s, it was anticipated that many racemic drugs might become marketed as single enantiomers through a “chiral switch” strategy. However, this approach has had limited success with NSAIDs [14]. Despite the lack of commercial interest in hydroformylation of these substrates, styrene continues to be a useful olefinic substrate for benchmarking the relative selectivity of new catalysts.

Allylic alcohols are versatile substrates for hydroformylation. Hydroformylation of allyl alcohol typically favors the linear regioisomer, and this reaction formed the basis of a route to manufacture 1,4-butanediol [15]. Landis recently reported the use of a chiral diazaphospholane for the asymmetric hydroformylation of allyl silyl ethers [16]. The TBDMS allyl ether, formed from reaction of allyl alcohol with TBDMSCl, was hydroformylated in 96%*ee* and 2:1 branched/linear to give the Roche aldehyde (**12**) which is a widely used chiral building block. High molar substrate/catalyst ratios (10,000:1) and low syngas pressures (15 psi) make this reaction potentially attractive for commercial development.

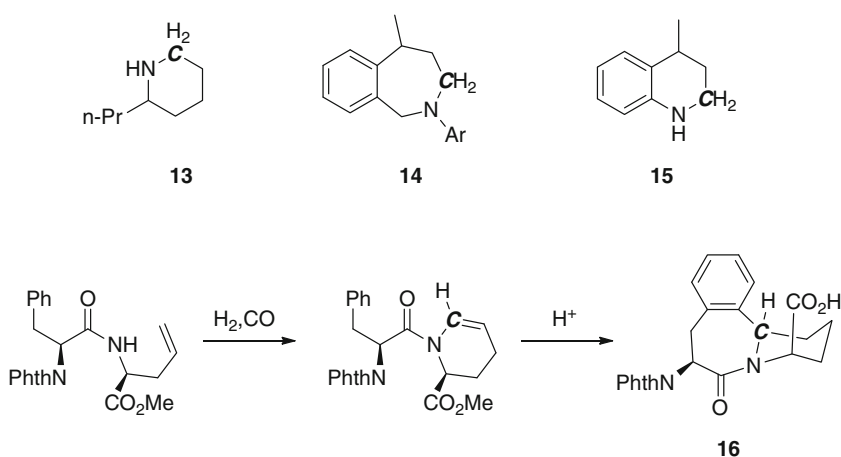


Highly selective asymmetric hydroformylation of vinyl acetate has been reported on 150-g scale by Landis and Klosin [17]. Reactions were performed in neat vinyl acetate using a chiral Rh-diazaphospholane catalyst at 100,000:1 molar

substrate/catalyst ratio to produce 2-(acetoxy)propanal in 96.8%*ee* and 139:1 branched/linear. The branched aldehyde was converted to chiral isoxazolines and imidazoles through its hydroximoyl chloride derivative.

Reductive amination of aldehydes prepared from hydroformylation is a useful route to amines. Botteghi, et al. reported the synthesis of racemic Tolterodine by sequential hydroformylation-reductive amination [18]. Hydroaminomethylation (tandem hydroformylation/reductive amination) has recently been used to prepare a wide variety of pharmaceutical compounds [19]. Representative examples are shown in Fig. 5. Hydroaminomethylation of 1,1-diarylethenes leads to 1-(3,3-diarylpropyl)amines, such as fenpiprane [20, 21]. Heterocyclic allylic amines undergo hydroaminomethylation to form pharmaceutically active diamines, such as etymemazine [22]. Ibutilide and fexofenadine have been prepared by hydroaminomethylation of 1-arylallyl alcohols in the presence of the requisite amines [23, 24]. Although none of these reactions has been developed into a commercial process, the widespread utility of the hydroaminomethylation reaction makes it likely that it will be used commercially

There are numerous reports of hydroformylation reactions where an amine substituent in the substrate condenses with the aldehyde product to form a heterocyclic ring (Fig. 6). Intramolecular hydroaminomethylation reactions are often referred to as cyclohydrocarbonylation reactions. A Cbz-protected homoallylic amine underwent cyclohydrocarbonylation with Rh-biphephos to form the natural product, ( $\pm$ )-coniine (Fig. 6, 13) [25]. Alper recently reported the formation the seven-membered ring of 2-benzazepines (Fig. 6, 14) by hydroformylation of 2-isopropenylbenzaldehydes in the presence of anilines [26]. Intramolecular hydroaminomethylation of 2-isopropenylanilines produces 1,2,3,4-tetrahydroquinolines (Fig. 6, 15) [27]. In some instances, the enamine derived from intramolecular condensation of the resulting aldehyde is desired. For example, the synthesis of a key intermediate (Fig. 6, 16) in the synthesis of a series of ACE inhibitors was



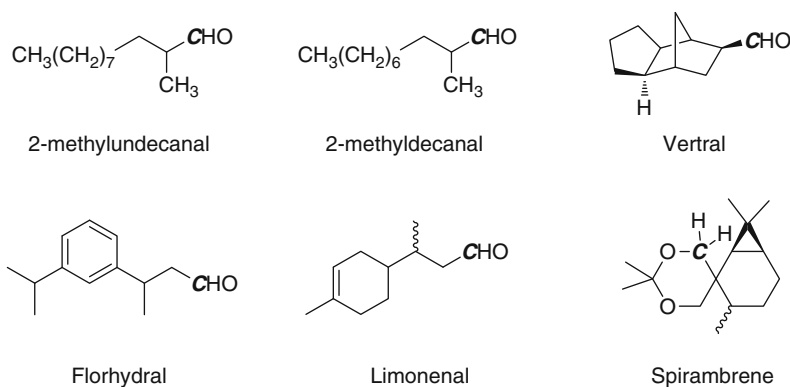
**Fig. 6** Compounds made using intramolecular hydroaminomethylation (cyclohydrocarbonylation)

accomplished by hydroformylation of a protected allylglycine derivative followed by intramolecular condensation [28]. Treatment of the enamine with acid resulted in cyclization to form **16**.

### 3 Fragrances

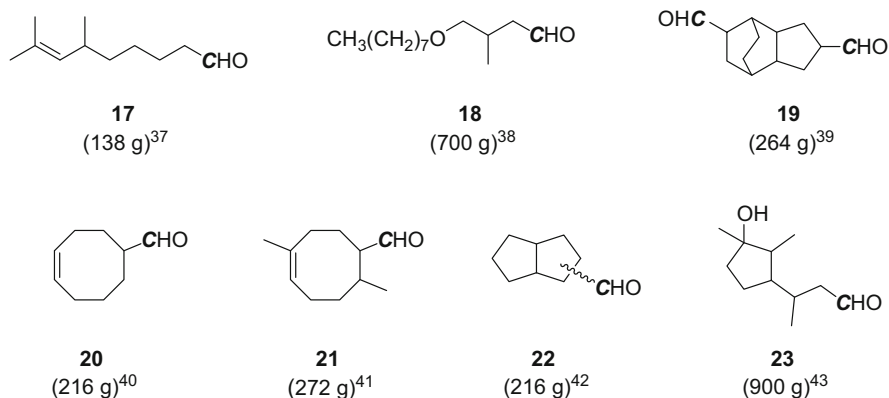
Hydroformylation is practiced in the fragrance industry where aldehydes are extensively utilized in perfumery (Fig. 7) [29]. 1-Decene is hydroformylated to a mixture of linear and branched undecanals. Condensation of the resulting C<sub>11</sub> linear aldehyde with formaldehyde gives 2-methyleneundecanal which is hydrogenated to 2-methylundecanal. The branched isomer from 1-decene hydroformylation, 1-methyldecenal, is also used in perfumery. Vertral® is produced by hydroformylation of *exo*-dicyclopentadiene with Rh<sub>2</sub>(2-Et-hexanoate)<sub>4</sub> to give the *exo*-monoaldehyde, followed by hydrogenation of the remaining olefinic bond [30]. Vertral has a green melon odor which is used in personal care products. Similarly, hydroformylation of neat 1,3-propenylbenzene with Rh-PPh<sub>3</sub> to give the monoaldehyde, followed by hydrogenation of the remaining C=C bond, is used for the preparation of Florhydal® [31]. Attempts to prepare enantiomerically pure Florhydal using asymmetric hydroformylation have led to low enantioselectivities [32]. In this case, asymmetric hydrogenation is a far more enantioselective (97%*ee*) route [33].

Conversion of terpenes to aldehyde derivatives by hydroformylation has been studied extensively. Hydroformylation of limonene is practiced commercially by Celanese [34]. Limonene aldehyde has a citrus odor and is used in soaps and lotions. Spirambrene® is manufactured by Givaudan and Vigon by hydroformylation of 2-carene [35, 36]. Tollens reaction of the resulting aldehyde gives a diol which is converted to the acetal with acetone. Spirambrene has a woody, spicy odor and is a component of perfumes.



**Fig. 7** Fragrances which are prepared commercially by rhodium-catalyzed hydroformylation





**Fig. 8** Recent applications of Rh-catalyzed hydroformylation in the fragrance industry. Mass of starting olefin is given in *parentheses*

Several additional hydroformylation applications from the fragrance industry have appeared recently in the patent literature. Examples which have been demonstrated on significant scale ( $>100$  g) are depicted in Fig. 8 [37–43]. Although there is no evidence these fragrance ingredients are currently manufactured using hydroformylation, given the scale of the reported reactions, it is likely that some of these reactions are of commercial interest.

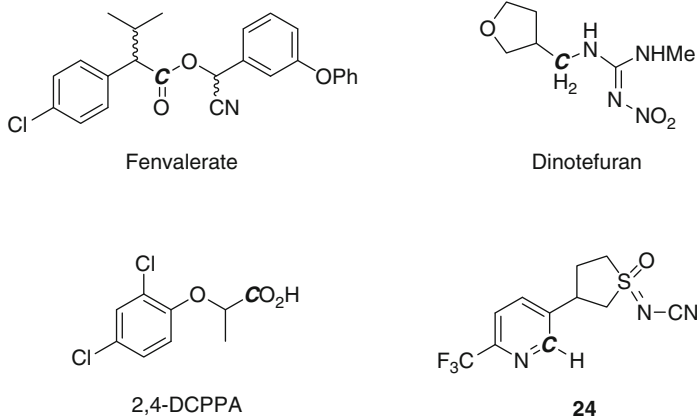
## 4 Agrochemicals

Hydroformylation does not appear to have been used in a commercial, agrochemical manufacturing process. Several examples of the use of hydroformylation in alternate synthetic routes to agrochemicals have been reported and are described below (Fig. 9). Hydroformylation of 2-methyl-1-*p*-chlorophenylpropene with  $\text{Rh-PPh}_3$  followed by oxidation gave 2-(*p*-chlorophenyl)-3-methylbutanoic acid which is an intermediate in the synthesis of the insecticide Fenvalerate (Fig. 9) [44].

The neonicotinoid insecticide, Dinotefuran (Fig. 9), developed by Mitsui has been prepared by hydroformylation of a symmetrical 1,3-dioxepin to give 3-(hydroxymethyl)tetrahydrofuran after deprotection [45]. Alternate routes to 3-(hydroxymethyl)tetrahydrofuran via hydroformylation of 2,3-dihydrofuran or 2,5-dihydrofuran have also been reported [46].

The insecticidal sulfoximine **24** (Fig. 9) was prepared by hydroformylation of 3-methylenetetrahydrothiophene with Rh-xantphos to give the linear aldehyde as a single regioisomer [47]. Conversion of the aldehyde to an enamine, followed by cyclization to form the pyridine ring and subsequent oxidation at sulfur, gave **24**.

Two reports of the use of asymmetric hydroformylation of aryl vinyl ethers to prepare enantiomerically enriched 2,4-DCPPA herbicide (Fig. 9) have appeared [48, 49]. Using Rh-(*S,R*)-Binaphos, the chiral aldehyde is produced in 72%*ee* but



**Fig. 9** Agrochemicals which have been prepared by rhodium-catalyzed hydroformylation

only 2:1 branched/linear. Although none of these reactions appear to be practiced commercially, they are significant applications of hydroformylation for the synthesis of important agrochemicals.

## 5 Conclusions

Fine chemical applications of rhodium-catalyzed hydroformylation have steadily increased over the past 20 years. Use of this chemistry in the fragrance industry appears to be relatively common. Pharmaceutical applications have started to increase as the technology becomes more familiar to process chemists. The commercial availability of ligands for both linear-selective hydroformylation and asymmetric hydroformylation has removed a barrier for screening catalysts by synthetic chemists. As additional large-scale examples of rhodium-catalyzed hydroformylation continue to be published, we expect this technology to be applied even more widely to fine chemical synthesis.

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Organometallics as Catalysts in the Fine Chemical  
Industry

Beller, M.; Blaser, H.-U. (Eds.)

2012, XII, 156 p., Hardcover

ISBN: 978-3-642-32832-9