Hydrogenation Processes in the Synthesis of Perfumery Ingredients

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ABSTRACT

Homogeneous catalytic hydrogenation has played an important role in the development of modern organic synthesis. Indeed, the discovery of highly regio- and stereoselective catalysts for C=C and C=O bonds reductions has allowed the efficient synthesis of optically active compounds. As the fragrance industry has turned to synthetic ingredients to fulfill the need for novel, cost-effective, and environment-friendly products, the use of catalytic processes are more and more in demand. In this Account, we thus highlight the application of catalytic hydrogenation in the synthesis of fragrance ingredients.

Introduction

Perfumery ingredients are found in many of today's consumer products, from female and male fine fragrances to household cleaning products. Their role since ancient times has been to help to cover the unpleasant smell of the base or body (e.g., soap or detergent, body malodors) and to provide a pleasing olfactive impression. These fragrance raw materials originate either from natural sources (e.g., terpenes, plant essential oils, animal secretions) or from chemical synthesis. The growing difficulties in obtaining sufficient quantities of natural ingredients and the continual emergence of new trends in the market have spearheaded the new ingredient strategy of the fragrance industry. The pressure to lower the costs and to use environment-friendly "green" chemical transformations has increased the need for stereoselective catalysis.[1] Several previous reviews have described the use of catalytic processes for the production of fragrance ingredients from natural[2] or synthetic[3] precursors.

Among the reactions that are catalyzed by transition metals, hydrogenation has been widely used in organic synthesis.[4] Moreover, the gaseous nature of the reactant allows the easy purification of the products with a minimum amount of waste. The catalytic homogeneous hydrogenations of C=C bonds were the first to be described almost 50 years ago. The pioneering work by Wilkinson and co-workers on rhodium catalysts[5] was rapidly followed by enantioselective variants described by Knowles[6] and Dang and Kagan.[7] These preliminary studies have led to intensive research on the synthesis of new chiral ligands[8] and mechanistic studies related to the improvement of the selectivity and efficiency of the catalysts.[9] Successful extensions have included the use of ruthenium complexes for chemoselective hydrogenation of functionalized C=C bonds[9] and of iridium complexes for the hydrogenation of isolated and unfunctionalized C=C bonds.[10] Catalysts for the hydrogenation of ketones also appeared during this time; especially ruthenium diphosphine/diamine complexes have proven to be excellent catalysts for the chemo- and enantioselective reduction of ketones.[11] The classical heterogeneous catalysts (e.g., Pd/C, Raney nickel) have also been used in enantioselective hydrogenation by the addition of chiral modifiers (e.g., tartaric acid, cinchona alkaloids).[4]

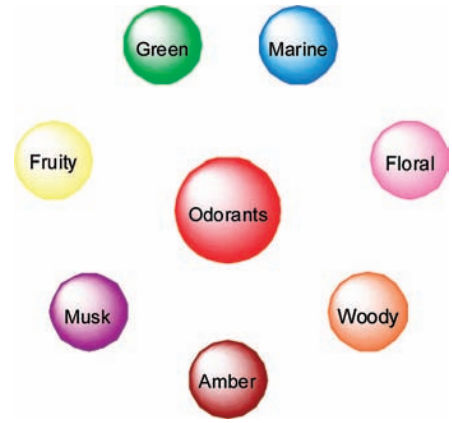

FIGURE 1. Odorant families.

Because the enantiomers of many odoriferous molecules differ in strength and in odor description,[12] the synthesis of the more appreciated isomer allows one not only to avoid the dilution effect by the non-desired one but also to put a smaller amount of the active ingredient into the final perfume. Nowadays, stereoselective hydrogenations of C=C and C=O bonds have become important tools for the industrial synthesis of fine chemicals using homogeneous rhodium, iridium, and ruthenium catalysts, as well as modified heterogeneous catalysts.[4] Catalytic hydrogenations of C=O bonds not only provide the desired product with a highly defined regio- and stereoselectivity but generate less waste, and these reactions are therefore cost-effective compared with the use of stoichiometric hydride reagents.

The chemistry of fragrance ingredients started at the end of the 19th century with the investigation of the odorant molecules responsible for the fragrance of violet flowers by Tiemann and Kruger,[13] and excellent reviews on fragrance chemistry have been recently published.[14] In this Account, examples of the use of hydrogenation processes in the synthesis of fragrance ingredients are described according to their olfactive family. Seven families of odorants were chosen: fruity, green, marine, floral, woody, amber, and musk (Figure 1).[15]

Lionel Saudan was born in Switzerland (26 February 1968) and received his Ph.D. degree from the University of Geneva with Professor E. P. Kündig in 1998 for his work on the asymmetric synthesis of new chiral amines. Then he joined the group of Professor J. M. Tour at the University of South Carolina and in 1999 followed him to Rice University working on the synthesis of new macromolecules. In 2000, he joined the R&D Corporate Division of Firmenich SA in Geneva and since then he has been working on the development of new processes based on organometallic catalysts for the synthesis of perfumery ingredients.

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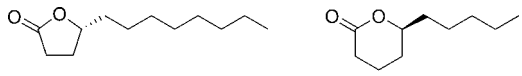
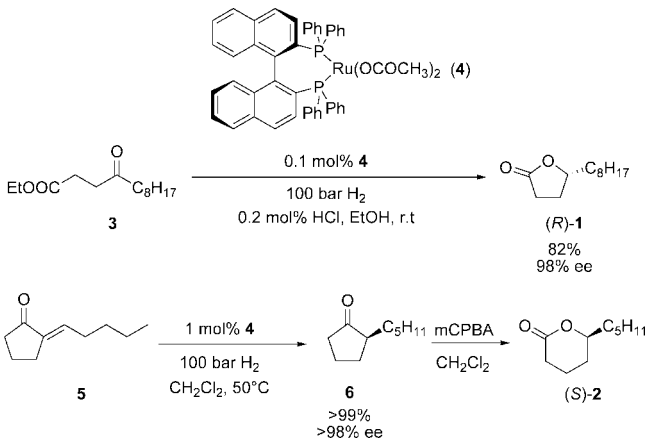


FIGURE 2. Examples of fruity odorants.

FIGURE 3. Examples of citrus odorants.

Scheme 1



Ingredients Responsible for Fruity Odor

Five-membered lactones (γ-lactones) and six-membered lactones (δ-lactones) with aliphatic side chains (Figure 2) have characteristic fruity notes of peach, apricot (γ-dodecalactones (e.g., **1**)), mango, passion fruit, strawberry, and coconut (δ-decalactones (e.g., **2**)).[16]

Ruthenium complexes with chiral diphosphines, used for the enantioselective hydrogenation of β-keto esters,[11] were also successfully applied for the hydrogenation of γ-keto esters (e.g., **3**), allowing the efficient synthesis of chiral 4-substituted γ-lactones (e.g., **1**). High yield and high enantioselectivity were obtained with ruthenium complex **4** incorporating the atropoisomeric diphosphine ligand (*R*)-[1,1′-binaphthalene]-2,2′-diylbis[diphenylphosphine] ((*R*)-BINAP; Scheme 1).[17]

Ruthenium complex **4** is also highly efficient for the enantioselective hydrogenation of the C=C bonds of 2-alkylidene-cyclopentanones (e.g., **5**).[18] Baeyer–Villiger oxidation, with retention of configuration, of these enantiomerically enriched 2-alkyl-cyclopentanones (e.g., **6**) furnished the desired 5-substituted δ-lactones (e.g., **2**) (Scheme 1).[19]

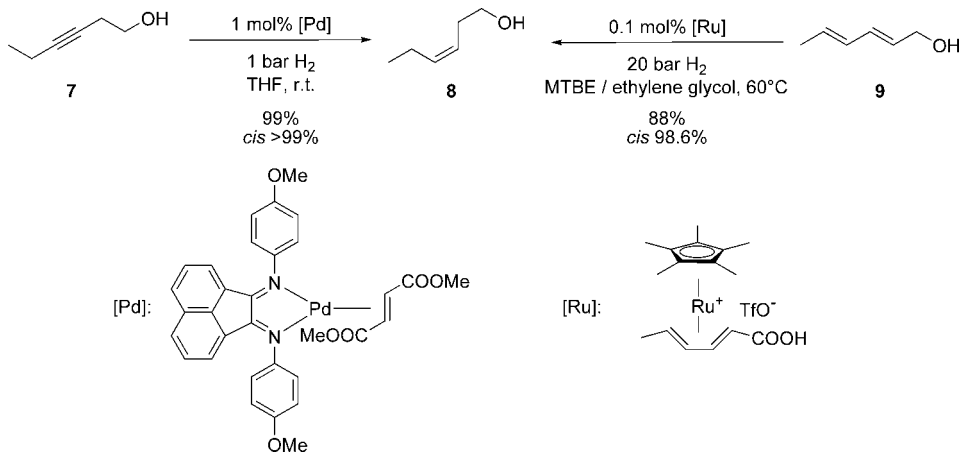
Ingredients Responsible for Green Odor

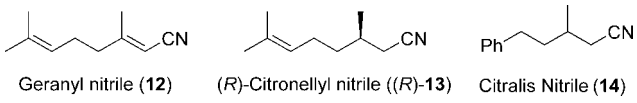
Leaf alcohol or *cis*-3-hexenol (**8**),[20] also known as pipol, is a commercially important green odorant, with a characteristic powerful, fresh, and intensively green, grassy odor. This powerful odorant has been found in many flowers, fruits, and vegetables (e.g., hyacinth, apple, tomato) and is mostly used, as are several derived esters, in floral or fruity fragrances. Heterogeneous Lindlar catalyst[21] and a homogeneous palladium catalyst[22] allowed the *cis*-selective partial hydrogenation of 3-hexyn-1-ol (**7**) into *cis*-3-hexenol (**8**) with high selectivity (Scheme 2). Another efficient synthesis of *cis*-3-hexenol (**8**) is the recently reported ruthenium-catalyzed 1,4-hydrogenation of sorbol (**9**) and sorbic acid derivatives.[23] Cationic Cp*-ruthenium complexes catalyze this reaction under mild conditions, and the *cis*-isomer is obtained with high selectivity (Scheme 2). This reaction was previously catalyzed by (η^6-arene)Cr(CO)$_3$ complexes,[24] which necessitated a much higher temperature and pressure unless complexes with labile ligands (e.g., naphthalene, acrylate) were used.[25]

An important subcategory of green notes in fragrances are citrus-type odorants. The most important representatives of this class are citral (**10**) and (*R*)-citronellal ((*R*)-**11**) (Figure 3).[26]

Citral (**10**) and citronellal (**11**), as are other aldehydes, are unstable in basic and oxidizing conditions, and therefore geranyl nitrile (**12**), citronellyl nitrile (**13**), and Citralis Nitrile (**14**)[27] have been successfully used to replace citrus-type aldehydes in such aggressive media (Figure 4). A strong citrus-type note characterizes these nitriles.

Scheme 2

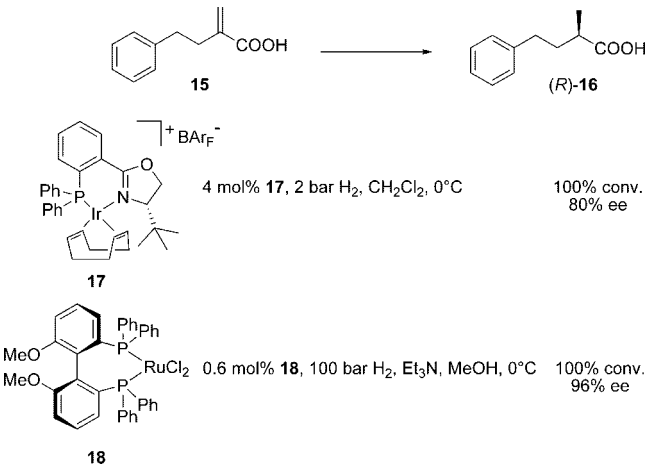




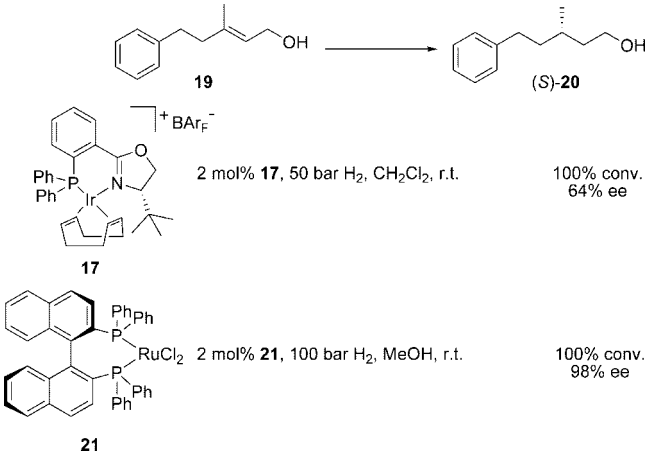
Geranyl nitrile (**12**) (*R*)-Citronellyl nitrile ((*R*)-**13**) Citralis Nitrile (**14**)

FIGURE 4. Examples of nitriles with citrus notes.

Scheme 3



Scheme 4



The evaluation of both enantiomers of Citralis Nitrile (**14**) has been reported.[28] Both enantiomers were prepared either via the enantioselective hydrogenation of phenylethylacrylic acid (**15**) (Scheme 3)[29] or via the enantioselective hydrogenation of allylic alcohol **19** (Scheme 4).[28] The resulting enantiomerically enriched acid **16** and alcohol **20** were then transformed into the desired nitrile. Chiral iridium and ruthenium complexes were tested as catalysts for these enantioselective hydrogenations. Good to high enantioselectivities were obtained in the hydrogenation of unsaturated acid **15** with either iridium complex **17** (80% ee) or ruthenium complex **18** (96% ee) (Scheme 3).

The same iridium catalyst **17** was also used in the catalyzed hydrogenation of allylic alcohol **19**, which gave the desired alcohol **20** with moderate enantioselectivity (46–69% ee). As observed with acid **15**, a much higher selectivity was obtained when a ruthenium catalyst was used (98% ee) (Scheme 4).

Ingredients Responsible for Marine Odor

Florhydral (**24**)[30] is an example of a marine odorant that is also characterized by floral notes. (+)-Florhydral (**24**) was found to be more powerful than (–)-Florhydral, which was nevertheless found to be more marine and typical of racemic Florhydral (**24**).[31] Racemic Florhydral (**24**) is prepared by rhodium-catalyzed mono-hydroformylation of *meta*-diisopropenylbenzene (**22**) followed by C=C bond hydrogenation of aldehyde **23** to give the desired product **24** (Scheme 5).[32] Enantioselective hydroformylation of olefin **25** to give enantiomerically enriched Florhydral (**24**) was also reported by the same authors, but very low enantioselectivity was obtained (5% ee) by using a catalyst generated *in situ* from (*R*)-BINAP and $HRh(CO)(PPh_3)_3$ (Scheme 5).

Ingredients Responsible for Floral Odor

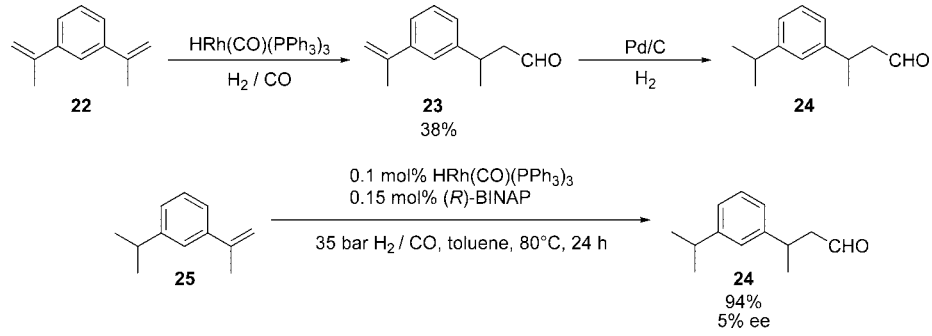
Three important subcategories exist for floral odorants: muguet, rose, and jasmin odorants.

Muguet Odorants. Muguet odorants are represented in perfumery by molecules that have olfactive properties reminiscent of the lily-of-the-valley flower. Lilial (**28**)[33] and dihydrofarnesol (**33**) are two important muguet aldehydes. The difference between the two enantiomers of Lilial is less pronounced, with the (*R*) enantiomer found to be more characteristic and powerful.[34] A direct synthesis of the more appreciated enantiomer by enantioselective nonracemizing hydrogenation of the corresponding cinnamaldehyde has never been reported. Nevertheless, either the enantioselective hydrogenation of unsaturated acid **26** catalyzed by ruthenium complex **4**[26] or the hydrogenation of allylic alcohol **29** catalyzed by iridium complex **30**[35] was used to prepare enantiomerically enriched Lilial (**28**) after functional group modifications of the corresponding acid or alcohol (Scheme 6).

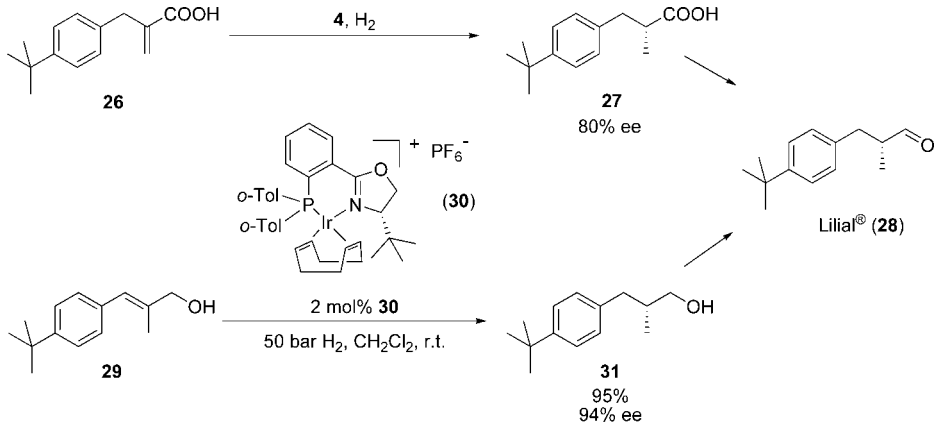
It is interesting to note that the hydrogenation of allylic alcohol **29** with a ruthenium complex has not been reported. In fact, there are only few examples of ruthenium-catalyzed enantioselective hydrogenation of allylic alcohols with substituent on the 2-position of the C=C bond. In contrast, they are numerous examples of hydrogenation of allylic alcohols without substituents on the 2-position and substituents on the 3-position.[10] For example, both enantiomers of dihydrofarnesol (**33**), a muguet odorant lacking the aldehyde function, were prepared by ruthenium-catalyzed hydrogenation of (2*E*,6*E*)-farnesol (**32**) (Scheme 7). (*S*)-(6*E*)-Dihydrofarnesol ((*S*)-**33**), also found in white cyclamen, was obtained with high enantioselectivity (89% ee) and was preferred olfactively over the (*R*) enantiomer.[26]

Rose Odorants. α-Damascone (**36**), an important ingredient of the rose ketones family, was not found in Bulgarian rose oil[36] but instead in green tea and tobacco as an almost racemic mixture.[37] Nevertheless, olfactive evaluation of both enantiomers revealed that (*S*)-α-damascone ((*S*)-**36**) is more powerful and more appreciated than the (*R*) enantiomer, which had a cork off-note.[12a] The enantioselective hydrogenation of ketone **34**

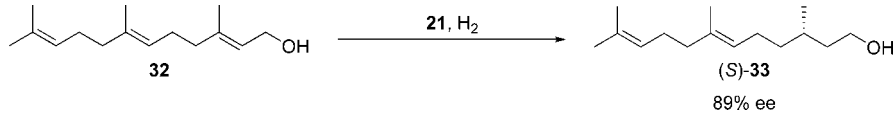
Scheme 5



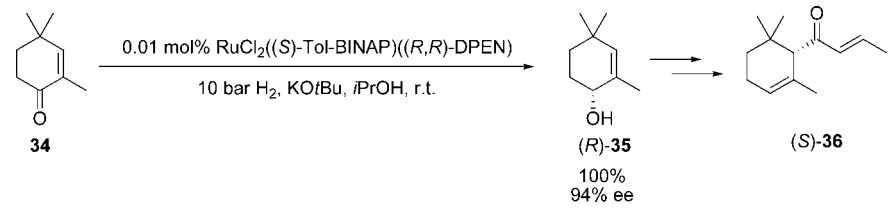
Scheme 6



Scheme 7

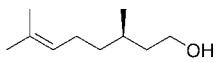


Scheme 8



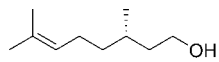
with $RuCl_2$((*S*)-Tol-BINAP)((*R*,*R*)-DPEN) gave allylic alcohol (*R*)-**35** in quantitative yield and with high enantioselectivity (94% ee) (Scheme 8).[38] Alcohol (*R*)-**35** was then transformed in several steps into (*S*)-α-damascone ((*S*)-**36**).[39]

Citronellol (**37**) is another important perfumery raw material with a rose note (Figure 5) and is used as starting material for other perfumery ingredients.[14b] The two enantiomers of citronellol have been evaluated olfactively and the odor of the *S* enantiomer was preferred as being closer to the odor of natural rose oil.[40]



(*R*)-**37**

"Slightly oily, light rosy-leafy, petal-like with irritating top note"



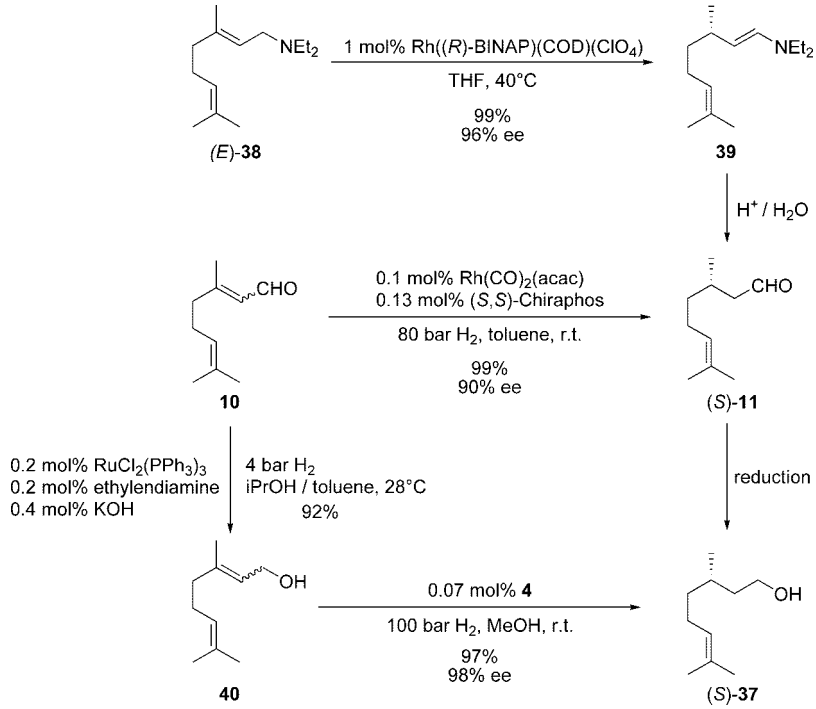
(*S*)-**37**

"Very fresh, light and clean rosy-leafy petal-like"

FIGURE 5. Difference in the olfactive perception of the enantiomers of citronellol.

(*R*)-Citronellol ((*R*)-**37**) was obtained by hydrogenation of natural citronellal, from citronella oil of low optical purity, over Raney nickel followed by distillation.[41] (*S*)-Citronellol ((*S*)-**37**) was isolated from rose oil in small amounts or obtained synthetically (Scheme 9). Indeed, (*S*)-citronellal ((*S*)-**11**) was obtained via the rhodium-catalyzed isomerization of neryl- or geranyl-amine ((*E*)-**38**) followed by hydrolysis of the chiral enamine **39**.[42] Then, reduction of (*S*)-citronellal ((*S*)-**11**) gave (*S*)-citronellol ((*S*)-**37**).[26] Recently, rhodium-catalyzed hydrogenation of neral ((*Z*)-**10**; *E*/*Z* 0.9/99.1) was also reported to give (*S*)-citronellal ((*S*)-**11**) in high enantioselectivity (90% ee) with the chiral diphosphine (*S*,*S*)-Chiraphos.[43] On the other hand, the hydroxyl-directed C=C bond hydrogenation of nerol or geraniol ((*E*)-**40**) catalyzed by ruthenium complex **4** gave access to (*S*)-citronellol ((*S*)-**37**) in high enantioselectivity (98% ee).[44] Moreover, nerol and geraniol were obtained

Scheme 9



in high yield and with a high selectivity by the chemoselective C=O hydrogenation of citral (**10**; *E*/*Z* 2/1) catalyzed by $RuCl_2(PPh_3)_3$ in presence of ethylene diamine.[45]

Jasmin Odorants. In jasmin flower oil, jasmone (**41**) and methyl jasmonate (**42**), the latter as a 93/7 mixture of *trans*/*cis* diastereoisomers, are two important odiferous constituents responsible for the typical odor of jasmin (Figure 6). During the structural elucidation of methyl jasmonate, it was found that only the (1*R*,2*S*)-*cis* isomer was responsible for the jasmin odor, the other isomers being substantially weaker or almost odorless.[46]

The rapid isomerization of the *cis*-jasmonate into the thermodynamic *trans* isomer, which is perceived as much weaker, and the relatively elevated price of the natural oil forced the fragrance companies to find a synthetic replacement for jasmin oil. The success of the industrial synthesis of a near-equilibrium mixture of the racemic *trans*/*cis* isomers of methyl dihydrojasmonate (**44**) was commercialized as Hedione (*trans*/*cis* 90/10) and allowed replacement of the natural extract (Figure 7).[47]

As in the natural methyl jasmonate (**42**), among the four isomers of methyl dihydrojasmonate (**44**) only the (1*R*,2*S*)-isomer was found to have an intense and distinct odor, while the presence of the other isomers acts as perception modifiers. Therefore, *cis*-enriched methyl dihydrojasmonate was produced either through continuous distillation, commercialized as Cepionate (25–30% *cis*-enriched),[20] or by using the advantageous neutral conditions provided by catalytic hydrogenation. Indeed, heterogenous hydrogenation of the vinylogous β-oxo ester **43** over Pd/C under neutral conditions gave the racemic *cis*-enriched methyl dihydrojasmonate, known as Hedione HC (62–70% *cis*-enriched).[48] More importantly, the homogeneous enantioselective hydrogenation gave the highly desired (1*R*,2*S*)-dihydrojasmonate (Paradisone; (1*R*,2*S*)-**44**),[49] with a high *cis*/*trans* selectivity (96/4) and a good enantioselectivity (65–88% ee) for the *cis*-isomer. This accomplishment was the result of the discovery of a coordinatively unsaturated ruthenium catalyst bearing a chiral diphosphine ligand that was able to hydrogenate the electron-deficient tetrasubstituted C=C bond of keto-ester **43**. A good enantioselectivity (65% ee) was obtained with (2*R*,5*R*)-Me-Duphos (**45**) as chiral ligand,[50] and after optimization of the reaction conditions and by using (R,S_{Fc})-Josiphos (**46**) as chiral ligand, a higher enantioselectivity (88% ee) was reached (Scheme 10). Ruthenium complexes with coordinating counteranions (e.g., **47**) known for C=C bond hydrogenation were inefficient with keto ester **43**, and it is only with the corresponding acid **48** that the desired *cis* product **49** was obtained with a

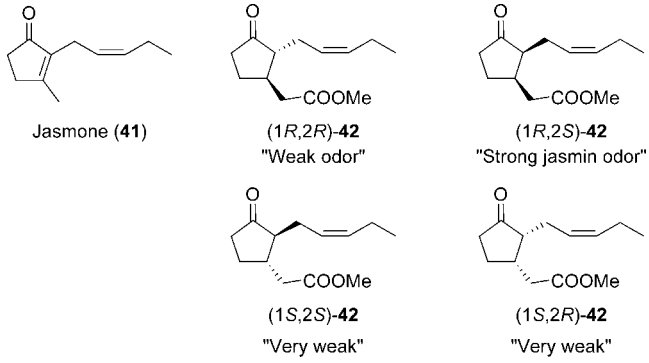


FIGURE 6. Examples of jasmin odorants.

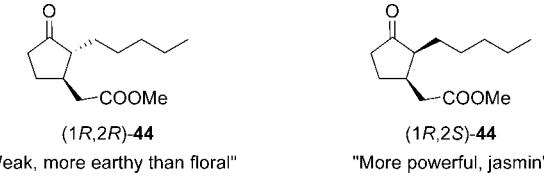
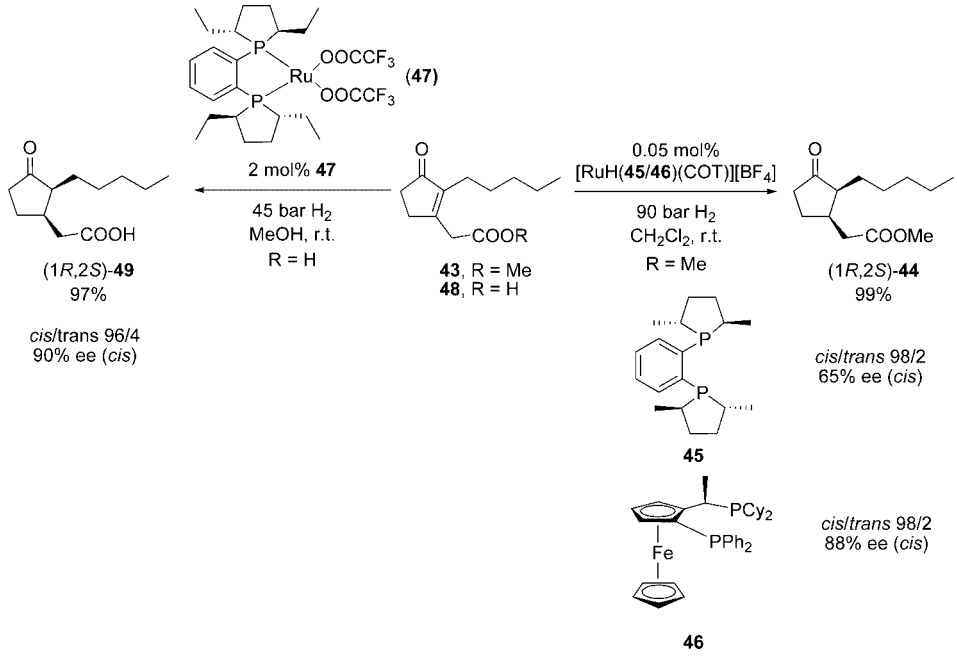
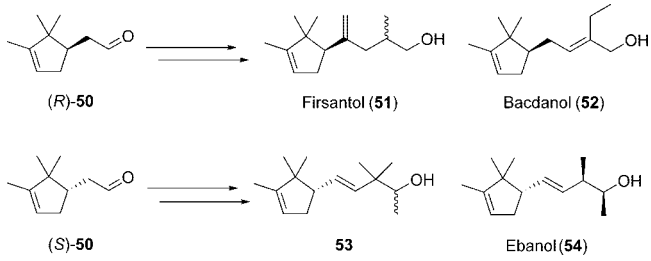


FIGURE 7. Methyl dihydrojasmonate.

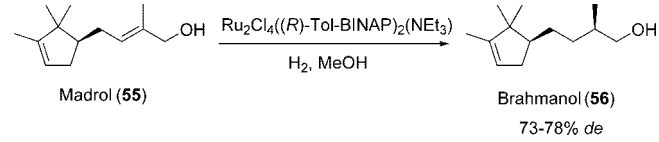
Scheme 10



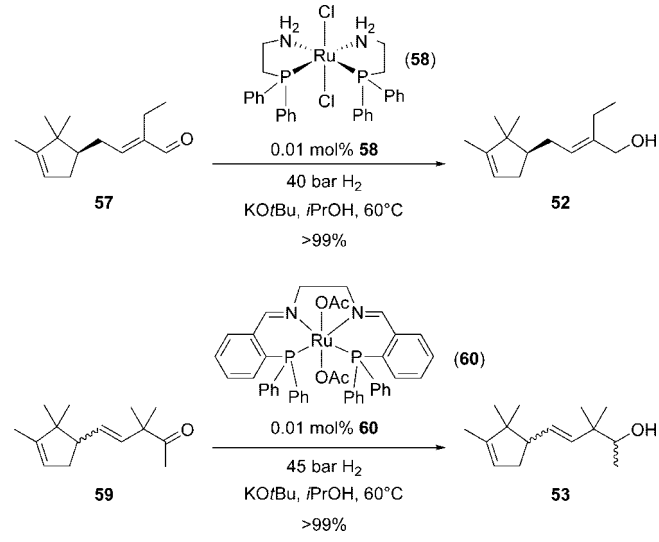
Scheme 11



Scheme 12



Scheme 13



high enantioselectivity (Scheme 10).[51] Despite the high enantioselectivity, this last approach was less attractive due to the subsequent esterification needed to obtain the desired keto-ester **44** without epimerization.

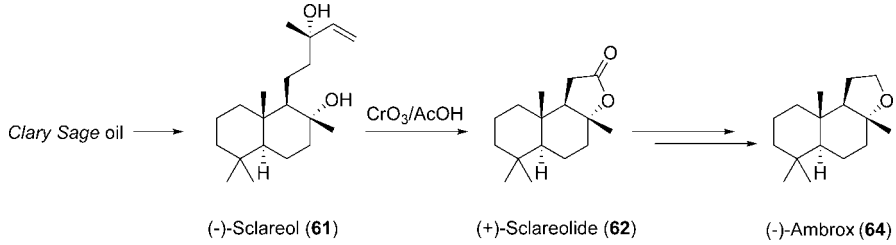
Ingredients Responsible for Woody Odor

Natural woody odorants are extracted from plants originating from South East Asia (e.g., Philippines, Java) and India. Due to the price increase of the natural oils and the rarity of the natural plants from which they are extracted, synthetic woody odorants have been developed. Amongst them, sandalwood odorants derived from α-campholenic aldehyde (**50**) (Scheme 11) have attracted much attention and have been the most successful. Both the (*R*) and (*S*) enantiomers of campholenic aldehyde (**50**) are readily prepared from the corresponding α-pinene enantiomer.[52] Depending on the side chain, the more appreciated isomers were derived from either (*R*)-campholenic aldehyde ((*R*)-**50**), as in the case of Firsantol (**51**)[53] and Bacdanol (**52**)[54] or (*S*)-campholenic aldehyde ((*S*)-**50**), as in **53**[55] and Ebanol (**54**).[56]

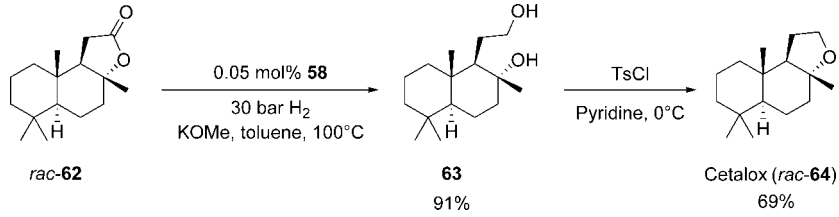
In the case of Brahmanol (**56**)[57] (Scheme 12), it was shown that the configuration of the ring stereogenic center did not play an important role in the odor perception, in contrast to the methyl group in the aliphatic side chain (β to the hydroxyl group). The diastereoisomers of Brahmanol (**56**) were prepared by ruthenium-catalyzed hydrogenation of Madrol (**55**),[58] another sandalwood odorant. The diastereomeric excess observed in this hydrogenation was between 73–78% with (*R*)-Tol-BINAP as the chiral ligand (Scheme 12).[26]

Ruthenium-catalyzed hydrogenation offers the possibility not only to introduce stereogenic centers but also to replace waste-generating reagents. For example, the reduction of C=O bonds was successfully performed by using hydrogenation instead of $NaBH_4$ in the preparation of the sandalwood odorants Bacdanol (**52**)[59] and **53**.[60]

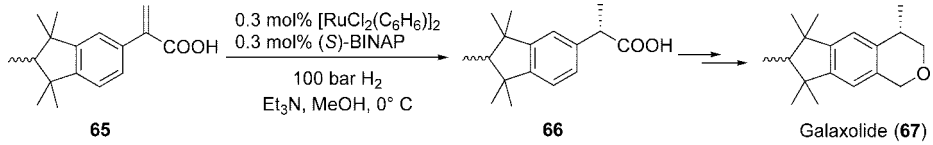
Scheme 14



Scheme 15



Scheme 16



Ruthenium amino-phosphine complex **58** and salen-type complex **60** catalyzed the H_2 reduction of aldehyde **57** and ketone **59**, respectively, with a high chemoselectivity and reactivity (Scheme 13).

Ingredients Responsible for Amber Odor

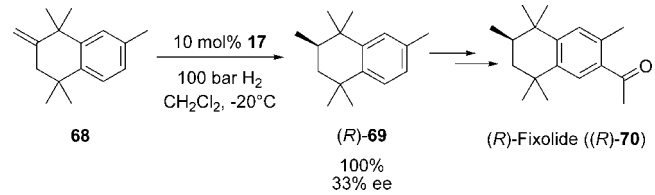
The smell of amber has been known since ancient times and is related to ambergris, a concretion formed in the intestinal tract of the sperm whale.[61] Among the various components of ambergris, the tricyclic ether (–)-**64**, known under the trade name Ambrox,[62] is the most important constituent responsible for the olfactive perception of the smell of amber. Ambrox ((–)-**64**) is appreciated for its powerful amber odor and substantivity. Optically active Ambrox ((–)-**64**), obtained via degradative oxidation of sclareol ((–)-**61**) (Scheme 14),[63] was later replaced by its racemate, known as Cetalox (*rac*-**64**),[64] which is olfactively very similar.

Several of the approaches towards the synthesis of Cetalox (*rac*-**64**) have often relied on the intermediacy of racemic lactone *rac*-**62**, followed by a hydride reduction, and then cyclization of the formed diol (**63**) to furnish the desired ether **64**.[65] Recently an efficient ruthenium-catalyzed dihydrogen reduction of esters was described.[66] This process was successfully applied to the reduction of *rac*-**62** to diol **63** in high yield (Scheme 15).[67]

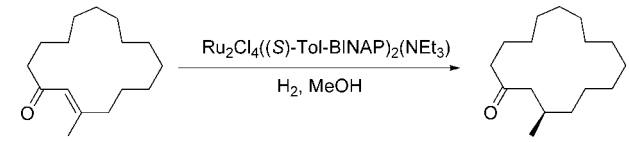
Ingredients Responsible for Musk Odor

Musk odorants have been perfumery ingredients since the beginning of the use of fragrances. They can be grouped into three main categories: nitro musks, polycyclic aromatic musks (e.g., Galaxolide (**67**)[68] and Fixolide (**70**)[69]),

Scheme 17



Scheme 18

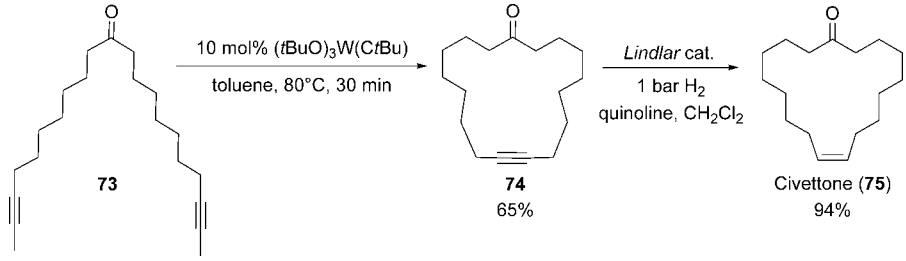


and finally the most expensive ones and the most sought after, the natural musks extracted from animals or plants (e.g., muscone (**72**) and civettone (**75**)).

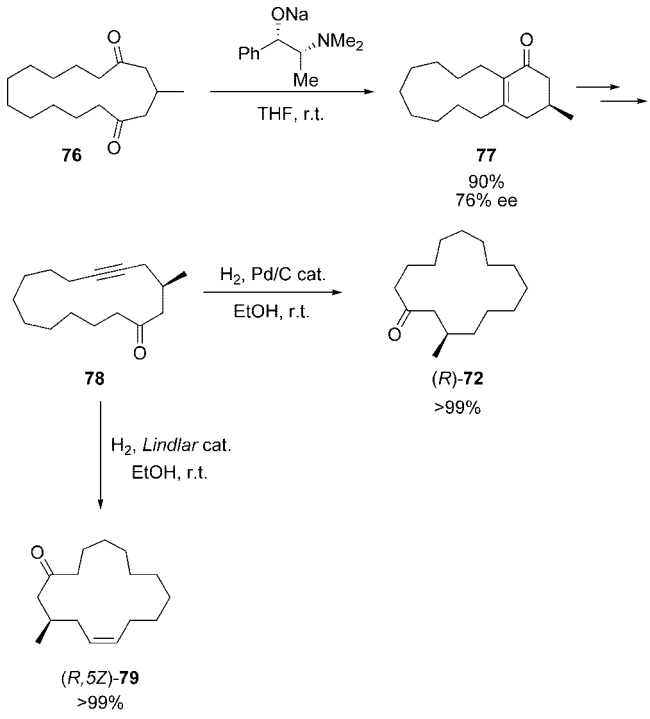
Galaxolide (**67**) possesses two stereogenic centers and all four stereoisomers have been prepared and olfactively evaluated.[70] Enantioselective hydrogenation was used for the synthesis of the more appreciated 4*S* isomers of galaxolide (**67**). A ruthenium catalyst generated *in situ* from $[RuCl_2(C_6H_6)]_2$, (*S*)-BINAP, and Et_3N (1 equiv) catalyzed the hydrogenation of the unsaturated acid **65** to give, in almost quantitative yield (94%), the (4*S*)-**66** acid with an optical purity (OP) of 89% (Scheme 16).[71] Further reduction of acid (4*S*)-**66** and cyclization gave the desired pair of diastereoisomers of Galaxolide (**67**) with the correct *S* configuration at the benzylic position.

The hydrogenation of the non-functionalized olefin **68** with an iridium complex was described as a catalytic

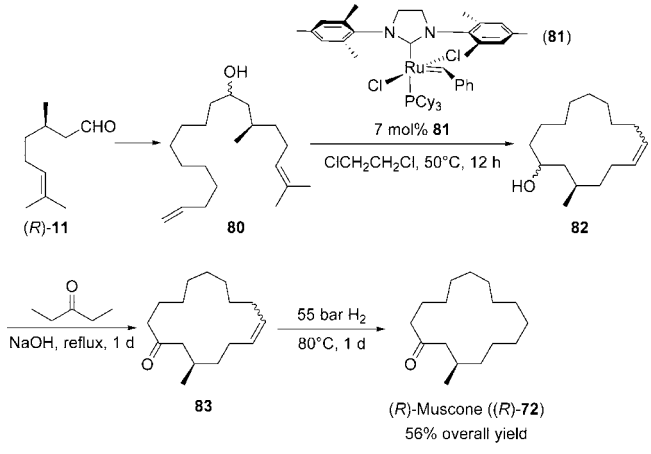
Scheme 19



Scheme 20



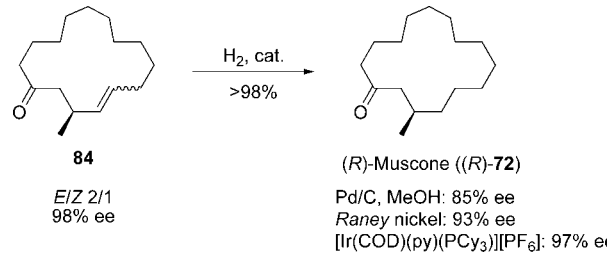
Scheme 21



approach to the more desired *S* enantiomer of the polycyclic musk Fixolide (**70**).[72] Disappointingly, olefin **68** was difficult to hydrogenate, and aromatic compound **69** was obtained with a low enantioselectivity (33% ee) in favor of the wrong isomer when using iridium complex **17** (Scheme 17).

The ready biodegradability of macrocyclic musks and the development of new cost-effective synthetic methods[73] resulted in an increased interest in this class of musk odorants. Muscone (**72**), a 15-membered macrocyclic ketone, possesses a stereogenic center at C-3 that was found to be *R* in the natural product isolated from the male musk deer. The *R* enantiomer was olfactively perceived as stronger with a very nice rich and powerful musky note, whereas the odor of the *S* enantiomer was found to be less interesting and less strong.[12a] Enantioselective hydrogenation of (*E*)-3-methyl-2-cyclopentadecenone ((*E*)-**71**) with ruthenium complex Ru_2Cl_4((*S*)-Tol-BINAP)$_2$(NEt_3) allowed the preparation of enantiomerically enriched (*R*)-muscone ((*R*)-**72**) with a high enantioselectivity (Scheme 18).[26] This high enantioselectivity was only obtained with the pure (*E*)-enone **71**, which was obtained by intramolecular aldol condensation followed by separation of the *E*/*Z* mixture of enones.[74]

Scheme 22



Two syntheses of macrocyclic musk molecules took advantage of the selective hydrogenation of alkynes into *Z*-olefins catalyzed by the Lindlar catalyst. Civettone (**75**) was prepared in high yield (65%) by a two-step sequence of alkyne metathesis, catalyzed by Schrock alkylidyne complex (*t*-BuO)$_3$W(C*t*-Bu), followed by partial hydrogenation of the C≡C bond into the *cis*-C=C bond (Scheme 19).[75]

The enantioselective aldol condensation of achiral diketone **76**, followed by an Eschenmoser fragmentation of bicyclic enone **77**, and finally hydrogenation of the macrocyclic alkyne **78** were the key steps for an efficient synthesis of (*R*,5*Z*)-muscenone (**79**) and (*R*)-muscone (**72**) (Scheme 20).[76]

Taking advantage of the development in ruthenium-catalyzed alkene metathesis, a very elegant synthesis of (*R*)-muscone (**72**) was reported and relied on several tandem ruthenium-catalyzed steps (Scheme 21).[77] Starting from optically active (*R*)-citronellal ((*R*)-**11**), alcohol **80** was cyclized with Grubbs second generation metathesis catalyst (**81**) to the corresponding macrocyclic alcohol **82**. Finally, two one-pot and consecutive ruthenium-catalyzed reactions, a transfer dehydrogenation followed by a C=C

bond hydrogenation, gave the desired musk ingredient (**72**) in an overall yield of 56%.

In the last step of this synthesis (Scheme 21) of (*R*)-muscone ((*R*)-**72**), it is noteworthy that the stereogenic center is ideally placed with respect to the C=C bond (**83**). Indeed in a different synthesis towards (*R*)-muscone ((*R*)-**72**), it was observed that during the C=C bond hydrogenation of enone **84**, where the C=C bond is closer to the stereogenic center, a partial racemization occurred.[78] This was probably due to the isomerization of the olefin prior to hydrogenation. The classical Pd/C catalyst gave the worst result, with up to 13% of racemization, and the authors found that the use of Crabtree's iridium catalyst, $[Ir(COD)(py)(PCy_3)][PF_6]$, provided (*R*)-muscone ((*R*)-**72**) with the minimum amount of racemization (Scheme 22).

Conclusion

This Account gives a survey of catalytic hydrogenations used in the synthesis of fragrance molecules. In most of the cases, each stereoisomer of the fragrance molecules exerts a different olfactive perception, and therefore diastereo- or enantioselective hydrogenations were used with success to prepare the most desired stereoisomer. The catalysts of choice up to now have been based on ruthenium complexes showing high activity and selectivity. Nevertheless, promising results were obtained with iridium and rhodium complexes, allowing different substrate scopes.

The increasing demand for fragrance ingredients of low cost and prepared with environment-friendly ("green") chemical processes has driven the search for new catalytic reactions. In the recent years, extremely active catalysts for the chemoselective dihydrogen reduction of esters, ketones, and aldehydes have been reported, opening the way for an efficient replacement of stoichiometric reducing agents (e.g., $LiAlH_4$). Moreover, very promising results have been recently reported with iron-[79] and copper-based[80] catalysts for the chemoselective hydrogenation of ketones, paving the way for catalysts based on inexpensive metals.

As the demand for natural fragrance ingredients is increasing, the use of existing and new hydrogenation methods will definitively continue to play an important role in the synthesis of these products due to their cost and waste effectiveness.

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Note Added after ASAP Publication: There was an error in Scheme 20 in the version published ASAP October 26, 2007. The corrected version published on November 20, 2007.

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