In Search of Nascent Musks ... or Not!

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The musk aroma has been valued by perfumers for what seems an eternity. Its characteristic odor is one of the few that can stand alone, unadorned by the supportive scents that are required to round out a wide variety of other odor types. In addition, the substantivity and stability of most musks have made them a sought-after material for performance-based products.

In the past 100 years, researchers from all of the major fragrance houses have attempted to identify the structural subunits required to provide the ultimate musk aroma chemical (see **Milestones in Musk Research**). These studies have encompassed everything from the strictly empirical to the qualitative structure activity relationship approach, and everything in between.

The on-going requirement for an even higher level of performance-based aroma chemicals has made the musks the most studied of all aroma chemicals, as customers continue to push for better cost performance in finished fragrances.

Early and serendipitous empirical studies provided the nitro musks, a cost-effective and powerful group of musks. The discovery of these materials fueled research in the 1960s and 1970s that led to a new class of synthetic musks, the polycyclics. As nitro musks fell into disfavor, polycyclics became the cost-effective workhorse in performance-based products and made inroads into the fine fragrance market as well.

While an extensive effort was carried out in macrocyclic musks, their high cost of manufacture guaranteed that their only significant use would be within fine fragrances. With the advent of molecular modeling software and more powerful computers, structure activity and conformational analysis were blended with empirical methods to identify the latest round of "super musks."

In this paper, I would like to convey our work at Union Camp and Bush Boake Allen in musk-related research over the past 15–20 years. The story takes us from innovative process chemistry on the two major polycyclic musks of our time into new, more powerful polycyclic musks, and back again into process research.

These latter discoveries came from a combination of empirical and structure-based approaches, with the additional caveat of minimizing the process cost from the onset. They paralleled and complemented the renewed interest of others in our industry. I refer to people such as Fehr,[15] Willis and Zazula,[16] Suzukamo and Sakito,[17] Helmlinger and Pesaro,[18] Frater et al.[19] and Christenson et al.,[20] whose work on lipophilicity and functional group related structural limitations both contributed to the general understanding and identified new, more powerful polycyclic musks.

## Process Development and Manufacture of Abbalide

After a long history in the manufacture of musk xylene, BBA turned its process chemists and engineers loose in the field of polycyclics. Our initial work in the 1980s was directed toward lowering the cost of manufacturing indanes and indanepropanols, key intermediates in the preparation of our isochroman musk, Abbalide[a] [8]. The original IFF process[21] for its counterpart Galaxolide[b] is shown in Scheme 1.

BBA sought to exploit its process skill capabilities advantageously to reduce overall manufacturing costs.

Scheme 1.
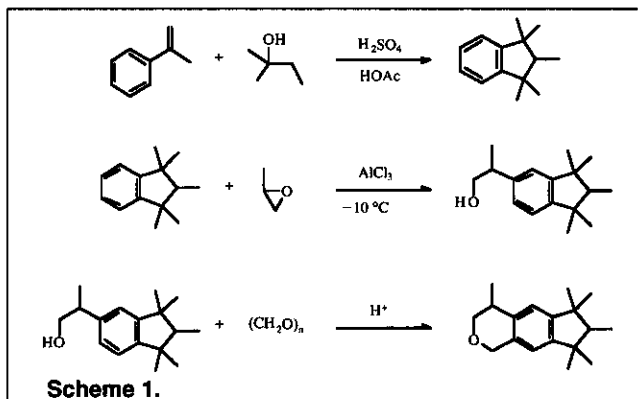
[a] Abbalide is hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran, a registered trade name of Bush Boake Allen, Montvale, NJ
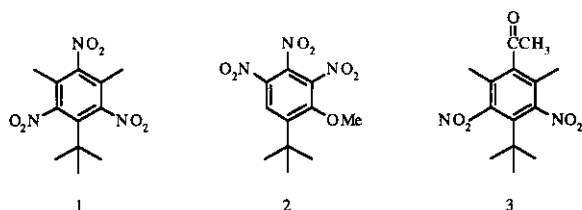[b] Galaxolide is hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran, a registered trade name of International Flavors & Fragrances, New York, NY
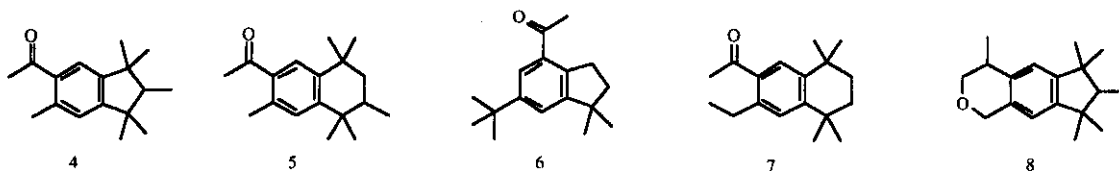
Milestones in Musk Research

Since the dawn of perfumery, musk has been both an integral and much sought-after component of fragrance mixtures. The structural identification and synthesis of both natural and synthetic musk compounds have peaked the curiosity of chemists for well over 100 years.

In a very early report of a synthetic sequence to a musk odorant in 1878, Kelbe[1] mentioned the weak musk odor of trinitro-para-cymene. However, Baur[2] elevated synthetic musk discovery to a new level shortly after his discovery in the late 1880s of the trinitro derivative of meta-methyl-tertiary-butylbenzene. In a brief span of time, he synthesized and patented the products that we know today as "musk xylene" [1], "musk ambrette" [2] and "musk ketone" [3]. Until re-

cently, these three materials comprised a very large portion of the total commercial musk market.

Additional discoveries in the synthetic musk field were subdued until the late 1940s when Carpenter and Easter[3,4] reported the first nitro-free benzenoid musk, 2,4-di-tertiary-butyl-5-methoxybenzal-dehyde. This sparked the most enduring and encompassing era of synthetic musk research in the fragrance industry, as chemists and their employers each sought to claim a piece of both history and profits. Out of this

activity, the field of polycyclic musks was spawned.

By the 1960s, a host of familiar musk products was on the aroma chemicals scene. The products included PFW's Phantolid[c] [4] and Tonalid[d] [5], IFF's Celestolide[e] [6] and Givaudan's Versalide[f] [7].

In the latter 1960s, another significant milestone occurred with the identification of isochromans as musk odorants. The best example of this type is IFF's Galaxolide[g] [8].

During this time of both empirical approach and musk odor theories,[5,6] process chemists were rapidly responding to the call for cost-effective syntheses of these exciting materials. As Friedel-Crafts chemistry became a better appreciated technique, it evolved into a workhorse for chemists in our field. With particular effectiveness in the area of cyclialkylation, researchers such as Beets, Bruson and Kroeger, Ipatieff and Wood used this chemistry to prepare indane and tetralin precursors and apply them to a wide range of new polycyclic musks.

The discovery that, under Bronsted and/or Lewis acid catalysis, neohexene and/or 2,3-dimethyl-1-butene reacted with para-cymene derivatives to form hexamethyltetralins[7-14] led to cost-effective, large-scale production of the already mentioned highly substantive PFW musk Tonalid [5].

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[c] Phantolid is 5-acetyl-1,1,2,3,3,6-hexamethylindan, a registered trade name of PFW Aroma Chemicals BV, Barneveld, The Netherlands; [d] Tonalid is 7-acetyl-1,1,3,4,4,6-hexamethyltetralin, a registered trade name of PFW Aroma Chemicals; [e] Celestolide is 4-acetyl-6-t-butyl-1,1-dimethylindane, a registered trade name of International Flavors & Fragrances, New York, NY, USA; [f] Versalide is 1,1,4,4-tetramethyl-6-ethyl-7-acetyl-1,2,3,4-tetrahydronaphthalene, a registered trade name of Givaudan-Roure SA, Geneva, Switzerland; [g] Galaxolide ia hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran, a registered trade name of International Flavors & Fragrances

Ferber and Goddard[22] first developed novel cyclialkylation technology to produce pentamethylindane from alpha-methylstyrene and 2-methyl-2-butene using phosphoric acid (Scheme 2). This process led to overall cost reductions in regard to raw materials, catalyst and capital employed.

This was followed by another novel BBA process by Ferber et al.[23] for the preparation of indanepropanols. It utilized refluxing solvent to remove heat effectively (Scheme 2). Reductions in capital cost and increased yield were the direct consequences of this improvement in process technology.

Scheme 2.

Sacrificial Olefin Methodology to Manufacture Tetralide

In the mid-1980s, we shifted our emphasis toward preparation of alkyl-substituted indanes and tetralins, intermediates in polycyclic musk manufacture. One target of this effort was Tetralide[c] [5], our counterpart to PFW's Tonalid,[d] which was prized for its very substantive behavior on cloth. To gain market entry, we required a technological edge, and we once again turned to process chemistry to provide it.
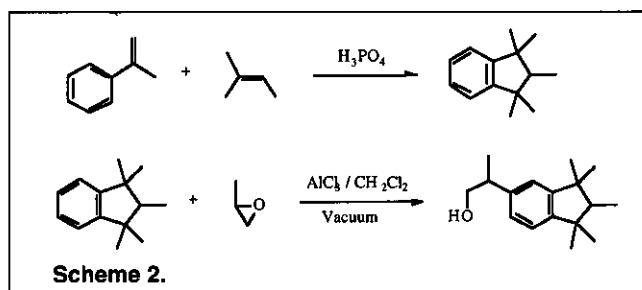
Acetylhexamethyltetrahydronaphthalene (Tetralide[5]) can be and has been prepared in a number of ways,[7-11,13,14,24-27] and involves two distinct synthetic steps, shown retro-synthetically in Figure 1.
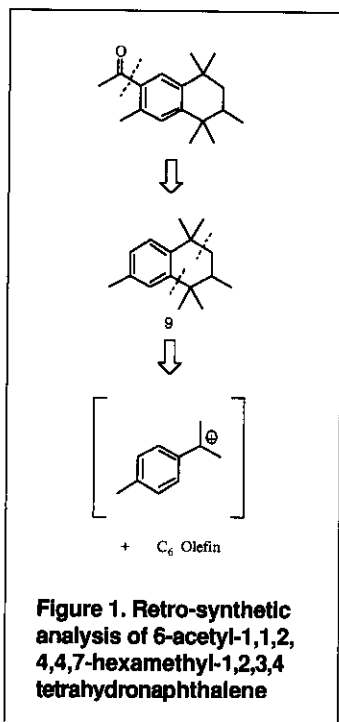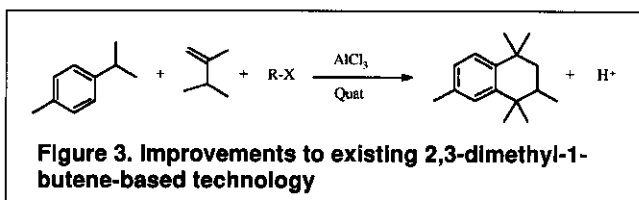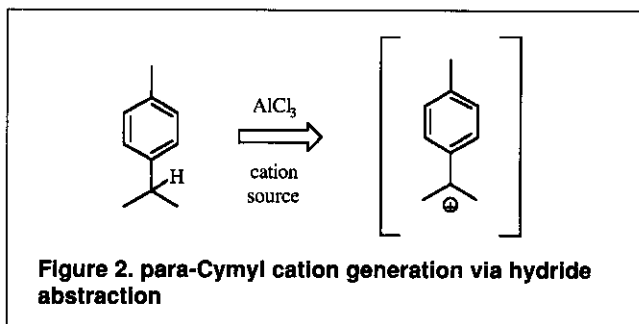
Most of the research in our industry has centered on the synthesis of 1,1,2,4,4,6-hexamethyltetrahydronaphthalene (HMT) [9]. The preparation of HMT can be envisaged from para-cymyl cation and an electron-rich C_6 olefin. The para-

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[c] Tetralide is 7-acetyl-1,1,3,4,4,6-hexamethyltetralin, a registered trade name of Bush Boake Allen, Montvale, NJ; [d] Tonalid is 7-acetyl-1,1,3,4,4,6-hexamethyltetralin, a registered trade name of PFW Aroma Chemicals BV, Barneveld, The Netherlands

Figure 1. Retro-synthetic analysis of 6-acetyl-1,1,2, 4,4,7-hexamethyl-1,2,3,4 tetrahydronaphthalene

cymyl cation electrophile has been prepared in a number of ways, most expediently from para-cymene itself via Lewis acid-catalyzed hydride abstraction (Figure 2).

Initially, we identified technology that provided operating improvements to existing methods.[28-30] Our application of quaternary ammonium salts to existing Sumitomo technology[12] improved both the consistency and yield of the process (Figure 3).

But we also recognized the need to prepare para-cymyl cation more efficiently using olefin alternatives to organic halides or excess C_6 alkene (Figure 4). We discovered a series of olefins that provided the necessary reaction properties. They had strong basicity to compete effectively for protons versus C_6 olefin. They also had poor nucleophilicity to inhibit the nucleus's participation in a parallel cyclialkylation.[31-36] Further, they did not, when protonated, compete with para-cymyl cation for alkylation by C_6 olefin, probably due to steric constraints realized in the olefin's approach. The best of these, 2,4,4-trimethyl-2-pentene, delivered excellent yields of HMT from readily available diisobutylene (Figure 5), when used in conjunction with either neohexene or 2,3-dimethyl-1-butene.

The story is even more satisfying when one realizes the interconnectedness of the cyclialkylating olefin progeny neohexene with its "sacrificial olefin" progenitor. BBA
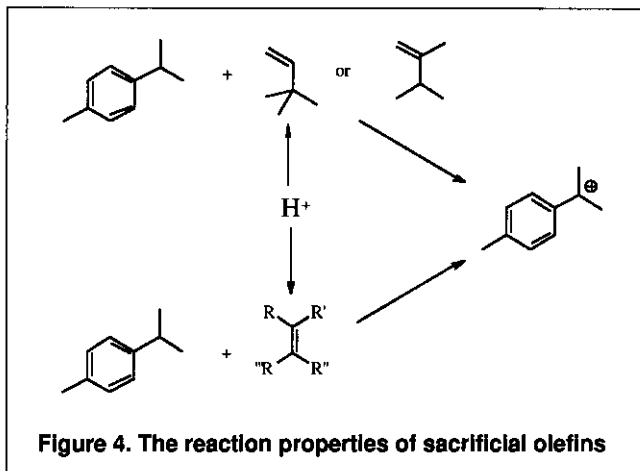

Figure 2. para-Cymyl cation generation via hydride abstraction

Figure 3. Improvements to existing 2,3-dimethyl-1-butene-based technology

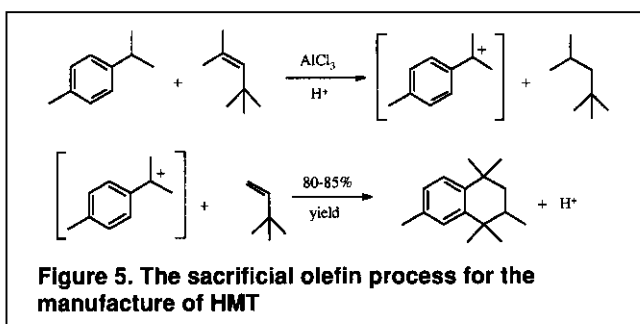**Figure 4. The reaction properties of sacrificial olefins**

Figure 5. The sacrificial olefin process for the manufacture of HMT

utilized this "sacrificial olefin" technology to manufacture Tetralide. Other concurrent Friedel-Crafts studies led to, among other things, a better understanding of indane/ tetralin interconversions.[37]

The Search for More Intense Polycyclic Musks

The synthetic understanding gained during our studies on indane and tetralin synthesis and interconversion begged the question as to whether other super musks, as yet unidentified, might be prepared using our technologies. So, in the late 1980s, BBA expanded efforts directed toward discovery of more powerful musk aroma chemicals. Concurrent research carried out by Fehr[15] on the impact of lipophilicity in polycyclic musks supported our belief that stronger musks might still be found, but his work went in a different direction. Our preliminary attempts to exploit recently gained process understanding gave rise to structures with reasonable musk odor, though not of the intensity and/or character desired.[38]

What they did generate was a host of materials for which we had strong sensory comparisons to fundamental structure. As we viewed the amassed information, we identified structural traits that we believed would give a better musk. Although some of this information contradicted earlier findings[15-20] about functional group accessibility, we con-
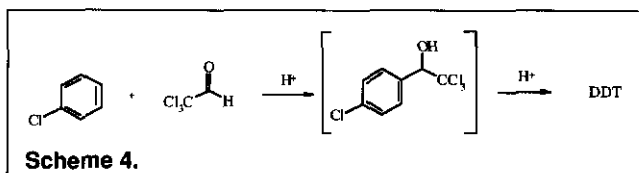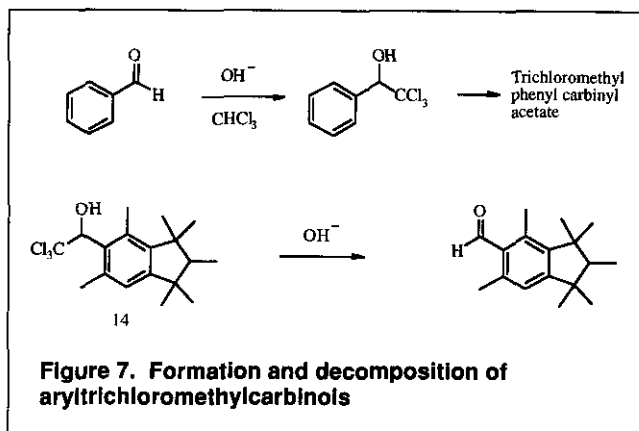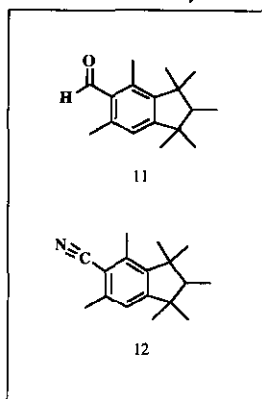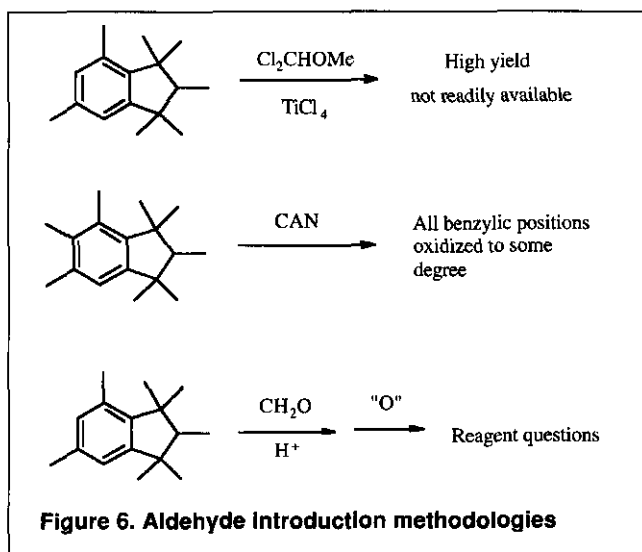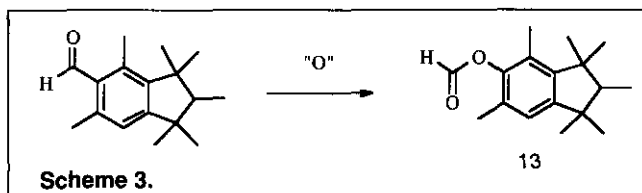
tinued our efforts, in part due to the fact that the product could be made from raw materials that were readily available at reasonable cost.

The result was a superior polycyclic musk, FHMI [11].[39,40] The material was as substantive as Tonalide, but with a far more natural and pleasing musk character than any other polycyclic musk. Its intensity was estimated to be four times that of Abbalide and twice that of Tetralide. The corresponding nitrile [12] was also an effective, stable musk aroma chemical.[41]

As might be anticipated from the structure, the other homologously substituted indanes had characteristic musk aromas.[42] In some of our early preparations of FHMI, we noticed the appearance of an additional GC peak over time. This turned out to be the formate ester [13] brought about by an unanticipated rearrangement of the aldehyde (Scheme 3). The formate ester was, surprisingly, a musk that was pleasant, yet slightly more volatile.[42] As a result of this unexpected finding, we subsequently identified a number of indane and tetralin formate ester musks.[43-46]

Development of Formylation Technology for Alkylated Aromatic Rings

Our major challenge in commercially preparing FHMI was the task of cost-effective formylation with alkylated aromatics. Therefore, we returned to our milieu of process organic chemistry.

Scheme 3.

Figure 6. Aldehyde Introduction methodologies

Figure 7. Formation and decomposition of aryltrichloromethylcarbinols

Scheme 4.

The most effective reagent—alpha,alpha-dichloromethyl methyl ether[47]—was not commercially available. Benzylic oxidation did not provide the required selectivity. Other formylation reagents were either too hazardous to contemplate using in an industrial setting, given our company's environmental awareness, or non-reactive for other than activated aromatic systems (Figure 6).

It had been known for some time that aldehydes reacted with chloroform under alkaline conditions to form trichloromethylcarbinols, such as the precursor to trichloromethyl phenyl carbinyl acetate. We reckoned that if we could prepare the corresponding trichloromethylcarbinol [14], it would easily collapse in the base to give FHMI (Figure 7).

Recent literature is dotted with examples of trichloromethylcarbinols as intermediates to alpha-hydroxy acids and esters,[48,49] but none of these gave commercially suitable routes to the desired carbinol.

A possible answer was suggested, ironically, by much earlier pesticide research. In the preparation of DDT, chlorobenzene reacts with chloral under acid catalysis to yield the product diaryl trichloroethane (Scheme 4).

The proposed intermediate is an aryltrichloromethylcarbinol analogous to the one that we desired. The issue became one of how to selectively protect the intermediate from a second arylation under the reaction conditions. We targeted Lewis acids as potential catalysts for two reasons. First, we knew, based on reports, that Bronsted acids would not provide adequate selectivity. Second, we hoped that the trichloromethyl group would coordinatively stabilize the Lewis acid: carbinol complex [15].
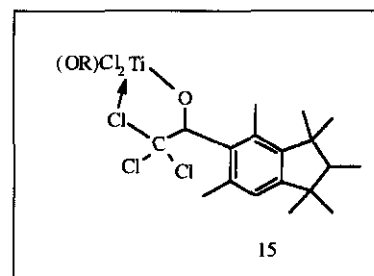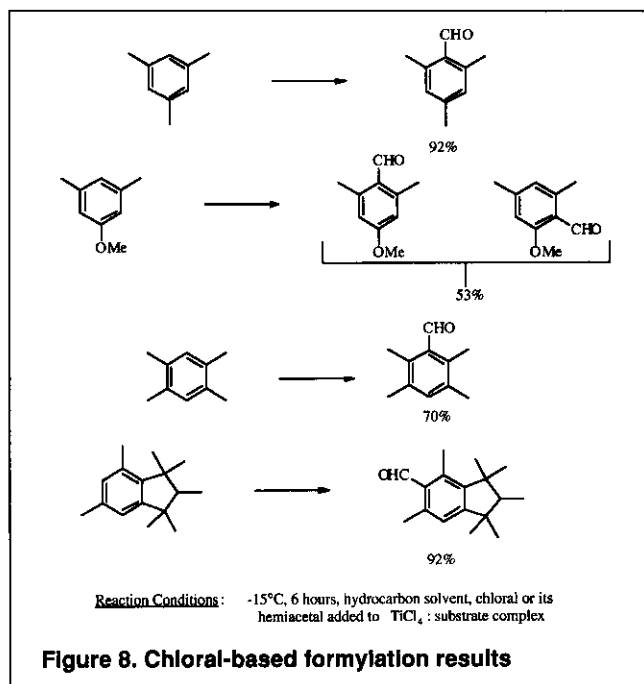
Figure 8. Chloral-based formylation results

We knew that we needed to reduce the acidity of the reaction or suffer the consequence of diarylation because of the inherent electron richness of our polyalkylated substrates. In addition, we were concerned about Lewis acid-catalyzed alkylbenzene rearrangements. In this re-gard, we utilized the hemiacetal of chloral to both enhance overall substrate solubility and reduce Lewis acidity.

We were pleasantly surprised with high selectivities to the carbinol, especially when titanium tetrachloride was used as the Lewis acid.[50] Subsequent treatment of the carbinol with a base provided high yields of the corresponding aldehyde[50] (Figure 8). The reasonable cost, coupled with the commercial availability of chloral, makes this route a practical manufacturing option for the formylation of alkyl substituted aromatic compounds.

Summary and Conclusions

In summary, I have highlighted research efforts carried out at Bush Boake Allen/Union Camp in support of musk aroma chemicals. These efforts were complementary to work carried out by others in our industry.

I have tried to show both the importance of solid process-development research and its creative synergism with product-related science. The result is highly cost-effective processes applicable to a range of commercial musks, a series of new musk aroma chemicals as well as a more complete understanding of the musk structure/odor relationship, and commercially viable formylation technology for alkylated aromatics.

This research has provided a sound foundation for BBA's continued exploration of new performance-based products.

References

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Note: The list of industry pioneers in the area of polycyclic musks in References 15-20 is certainly not all-inclusive; many others have contributed to the overall musk effort.

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