FRIEDEL-CRAFTS REACTIONS

1. Introduction

In 1877, at the Sorbonne in Paris, Charles Friedel and his American associate, James Mason Crafts, showed that anhydrous aluminum chloride could be used as a condensing agent in a general synthetic method for furnishing an infinite number of hydrocarbons. In work stretching over 14 years, they extended their discoveries of the catalytic effect of aluminum chloride in a variety of organic reactions: (*1*) reactions of alkyl and acyl halides and unsaturated compounds with aromatic and aliphatic hydrocarbons; (*2*) reactions of acid anhydrides with aromatic hydrocarbons; (*3*) reactions of oxygen, sulfur, sulfur dioxide, carbon dioxide, and phosgene with aromatic hydrocarbons; (*4*) cracking of aliphatic and aromatic hydrocarbons; and (*5*) polymerization of unsaturated hydrocarbons. The diversity of reactions is astounding.

Many important industrial processes such as the production of high octane gasoline, ethylbenzene (eventually leading to polystyrene), synthetic rubber, plastics, and detergent alkylates are based on Friedel-Crafts chemistry. The scope of the reactions is extremely wide as they form a large part of the more general field of electrophilic reactions, the class of reactions involving electron deficient carbocationic intermediates. The published literature is very extensive, and for more detailed information, monographs (1, 2) and other comprehensive reviews (3–5) should be consulted (see also ALKYLATION; ALUMINUM COMPOUNDS; BORON COMPOUNDS; CATALYSIS).

The observation that aluminum chloride [7446-70-0] is not the only specific catalyst in the reaction was included in the first papers of Friedel and Crafts. Ferric chloride [7705-08-0] and zinc chloride [7646-85-7], as well as the double salt sodium aluminum chloride [7784-16-9], were employed *inter alia,* but were generally found less reactive. In many Friedel-Crafts reactions substantial amounts of $AlCl_3$ (or related halides) must be used, greatly exceeding what would be needed as catalyst. The reason for this is that the Lewis or Brønsted acids are tied up, either forming molar complexes with the reagents and products (such as carbonyl compounds, etc) or participating as counter ions in so-called "red oil" formation (systems composed of carbocationic complexes resulting from protonation or alkylation of aromatics or aliphatic unsaturated systems). This was a significant drawback of Friedel-Crafts chemistry. The emergence of highly acidic solid catalysts, such as H-ZSM-5, an acidic form of Zeolite (aluminosilicate), or Nafion-H (perfluoroalkanesulfonic acid polymer developed by Du Pont), now allows Friedel-Crafts reactions without such complex formation. Reagents are passed through heterogeneous solid acid catalysts, representing a significant advance in the practical application of Friedel-Crafts reactions.

To define Friedel-Crafts reactions, it was necessary to come to a clear understanding that not one but a number of electrophilic reactions are classified as Friedel-Crafts type (2). Friedel-Crafts-type reactions are generally considered to be any substitution, isomerization, elimination, cracking, polymerization, or addition reaction that takes place under the catalytic effect of Lewis acid-type acidic halides (with or without cocatalysts) or Brønsted acids. Friedel-Crafts reactions are not limited to the formation of carbon–carbon bonds but also lead to formation or cleavage of carbon–oxygen, carbon–nitrogen, carbon–sulfur, carbon–halogen, carbon–metals, and many other types of bonds. Friedel-Crafts reactions can be divided into two general categories: alkylations and acylations. Within these two broad areas there is considerable diversity.

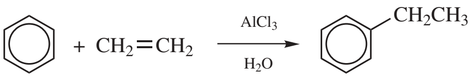
2. Alkylation

2.1. Alkylation of Aromatic Compounds. In the usual Friedel-Crafts alkylation of aromatics, a hydrogen atom of the aromatic nucleus is replaced by an alkyl group through the interaction of an alkylating agent in the presence of a catalyst. The most frequently used alkylating agents are alkyl halides, alkenes, alkynes, alcohols, esters (of carboxylic and inorganic acids), ethers, aldehydes and ketones, cycloalkanes and cycloalkenes, thiols (mercaptans), sulfides, amines (via diazotization), thiocyanates, and the like. The overall reactions using alkyl halides and alcohols as alkylating agents in the presence of aluminum chloride can be written as follows:

$$C_6H_6 + RX \xrightarrow{AlCl_3} C_6H_6R + HX$$

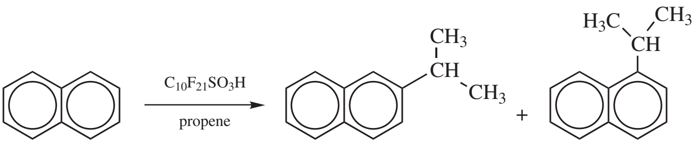
$$C_6H_6 + ROH \xrightarrow{AlCl_3} C_6H_6R + H_2O$$

Friedel-Crafts alkylation using alkenes has important industrial applications. The ethylation of benzene with ethylene to ethylbenzene used in the manufacture of styrene, is one of the largest scale industrial processes. The reaction is done under the catalysis of $AlCl_3$ in the presence of a proton source, ie, H_2O, HCl, etc, although other catalysts have also gained significance.



Propylation of benzene with propylene, catalyzed by supported phosphoric acid (or related catalysts such as $AlCl_3$), gives cumene [98-82-8] in another important industrial process. Cumene (qv), through the intermediacy ofcumene hydroperoxide, is used in the manufacture of phenol (qv). Resorcinol similarly can be made from *m*-diisopropylbenzene (6).

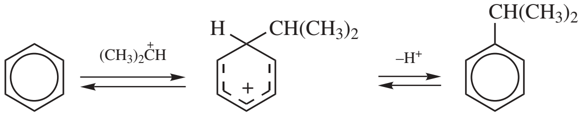
Tertiary, benzyl, and allylic nitro compounds can also be used as Friedel-Crafts alkylating agents; eg, reaction of $(CH_3)_3CNO_2$ (2-nitro-2-methyl propane [594-70-7]) with anisole in the presence of $SnCl_4$ gives 4-*t*-butylanisole [5396-38-3] (7). Solid acids, such as perfluorodecanesulfonic acid [335-77-3], and perfluorooctanesulfonic acid [1763-23-1] have been used as catalysts for regio-selective alkylations (8).



2.2. Mechanism.

The mechanism of alkylation and of other related Friedel-Crafts reactions is best explained by the carbocation concept. The alkylation of benzene with isopropyl chloride may be used as a general example:

$$(CH_3)_2CHCl + AlCl_3 \rightleftharpoons [CH_3\overset{+}{C}HCH_3][AlCl_4]^-$$



Lewis acid catalysts, such as $AlCl_3$ or BF_3, coordinate strongly with nonbonded electron pairs but they interact only weakly with bonded electron pairs. Therefore, *n*-donor reagents, such as alkyl halides, can react with Lewis acid catalysts even under complete exclusion of moisture or any other proton source:

$$RX + MX_3 \rightleftharpoons R^{\delta+}{-}{-}{-}{-}X{-}{-}{-}{-}MX_3^{\delta-} \rightleftharpoons [R^+]MX_4^-$$

However, strong protic acid catalysts are needed when π- or σ-donor alkylating agents are used to produce carbocationic or highly polarized donor-acceptor-complexes as the reactive alkylating intermediates:

$$RCH{=}CH_2 + HMX_{4\text{ or }6} \rightleftharpoons R^+CHCH_3MX^-{}_{4\text{ or }6}$$

$$R_2CHCH_3 + HMX_{4\text{ or }6} \rightleftharpoons R_2^+CHMX^-{}_{4\text{ or }6} + CH_4$$

In superacidic media, the carbocationic intermediates, which were long postulated to exist during Friedel-Crafts type reactions (9–11) can be observed, and even isolated as salts. The structures of these carbocations have been studied in high acidity–low nucleophilicity solvent systems using spectroscopic methods such as nmr, ir, Raman, esr, and x-ray crystallography.

2.3. Dealkylation, Transalkylation, and Disproportionation. The action of aluminum chloride also removes alkyl groups from alkylbenzenes (dealkylation, disproportionation) (12). Alkylbenzenes, when heated with $AlCl_3$, form mixtures of benzene and polyalkylated benzenes:

$$2\ C_6H_5R \xrightarrow{AlCl_3,\ \text{heat}} C_6H_6 + C_6H_4R_2,\ \text{etc}$$

The tendency of alkyl groups to disproportionate is as follows: $CH_3 < C_2H_5 < n\text{-}C_3H_7 < i\text{-}C_3H_7 < tert\text{-}C_4H_9$ (13).

For example, in the industrially important alkylation of benzene with ethylene to ethylbenzene, polyethylbenzenes are also produced. The overall formation of polysubstituted products is minimized by recycling the higher ethylation products for the ethylation of fresh benzene (14). By adding the calculated equilibrium amount of polyethylbenzene to the benzene feed, a high conversion of ethylene to monoethylbenzene can be achieved (15) (see also XYLENES AND ETHYLBENZENE).

2.4. Polyalkylations. It had been assumed (16) that the tendency toward poly-substitution during Friedel-Crafts alkylation is due to the greater reactivity of the initially produced alkylbenzenes toward further substitution. This kinetic effect, however, has been shown to be limited; the alkyl groups on a benzene nucleus have only a small activating effect on the reaction rate. The actual alkylation occurs in a heterogeneous reaction system, specifically in the acidic catalyst layer, and the reason for polysubstitution is the preferential extraction of the initial alkylates into this catalyst layer allowing ready further alkylation (17). The tendency toward polysubstitution may be minimized by the use of a mutual solvent for both the hydrocarbon and catalyst, by high speed stirring, by operating in the vapor phase or at a temperature sufficiently high for the aluminum chloride to be soluble in the hydrocarbon layer.

2.5. Orientation. If more than one alkyl group is introduced into benzene the question of orientation arises. Alkylation in the presence of aluminum chloride and other Friedel-Crafts catalysts usually yields a considerable proportion of meta dialkylbenzenes, as well as the expected ortho and para isomers (16). In general, the more drastic the reaction conditions (longer reaction time and high temperature, large amount of catalyst, absence of solvent, etc), the greater is the tendency toward the formation of meta derivatives. Although electron releasing groups such as alkyl, amino, etc, groups on the aromatic ring direct electrophiles preferentially to the ortho and para positions, the meta isomers are usually the thermodynamically favored products, and hence are formed via secondary isomerization particularly under more forcing conditions.

Shape selective catalysts, such as Zeolites of the H-ZSM-5 type, are capable of directing alkyl groups preferentially to the para position (18). The ratio of the catalyst to the substrate also plays a role in controlling the regiochemistry of the alkylations. For example, selective alkylation of anilines at the para position is achieved using alkylating agents and $AlCl_3$ in equimolar ratio (19).

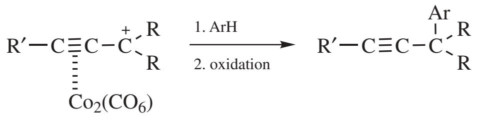
2.6. Isomerization. In the course of alkylation two different types of isomerizations can take place. The first involves the alkylating agent which may undergo rearrangement and is generally converted to a more highly branched isomer. Thus the alkylation of benzene with *n*-propyl chloride in the presence of aluminum chloride yields *n*-propylbenzene and isopropylbenzene (cumene), and with *n*-butyl chloride *see*-butylbenzene is formed. Under the usual conditions of a Friedel-Crafts alkylation, the alkyl group rearrangement takes place via carbocations favoring the formation of more stable highly branched species, ie, primary $\longrightarrow$ secondary $\longrightarrow$ tertiary.

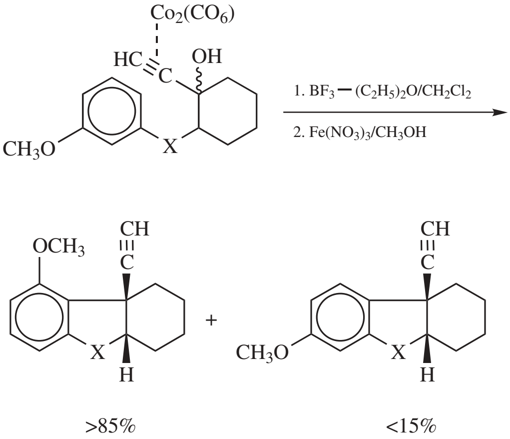
Alternatively the alkylated aromatic products may rearrange. *n*-Butylbenzene [104-57-8] is readily isomerized to isobutylbenzene [538-93-2] and *sec*-butylbenzene [135-98-8] under the catalytic effect of Friedel-Crafts catalysts. The tendency toward rearrangement depends on the alkylating agent and the reaction conditions (catalyst, solvent, temperature, etc).

Because of isomerization, alkylation of benzene with tertiary alkyl halides can also yield secondary alkylbenzenes rather than only tertiary alkylbenzenes (20). For example, the *tert*-hexylbenzene, which is first formed by the reaction of benzene with 2-chloro-2,3-dimethylbutane and $AlCl_3$ isomerizes largely to 2,2-dimethyl-3-phenylbutane by a 1,2-CH_3 shift. With ferric chloride as the catalyst, *tert*-hexylbenzene does not undergo isomerization and is isolated as such.

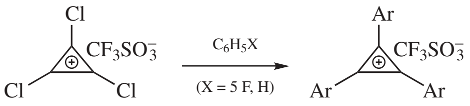
The isomerization of dialkylbenzenes generally results in a considerable increase of the meta isomer, because as thermodynamically controlled equilibrium is approached the relative ratios of the ortho, meta, and para isomers are predicted by their relative thermodynamic stabilities (21). Similar thermodynamically controlled equilibria are obtained in the treatment of dihalo- (22) and polyhalobenzenes, as well as haloalkylbenzenes (23) with Friedel-Crafts catalyst systems. Aryl groups migrate in a way similar to the migration of alkyl and cycloalkyl groups.

2.7. Preformed Carbocationic Intermediates. Propargyl cations stabilized by hexacarbonyl dicobalt have been used to effect Friedel-Crafts alkylation of electron-rich aromatics, such as anisole, *N,N*-dimethylaniline and 1,2,4,-trimethoxybenzene (24). Intramolecular reactions have been found to be regio and stereo-selective, and have been used in the preparation of derivatives of 9*H*-fluorenes and dibenzofurans (25).

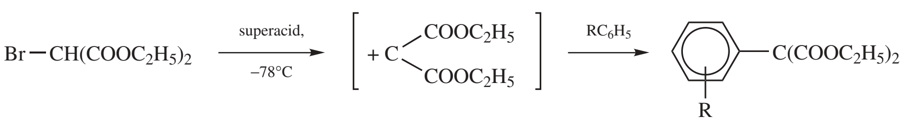




The Friedel-Crafts alkylation of aromatics with the resonance-stabilized trichlorocyclopropenium triflate offers a synthetic pathway to triaryl cyclopropenium salts (26). The trichlorocyclopropenium ion has also been shown to undergo Friedel-Crafts reaction with alkenes and alkynes to give trivinyl and tri(halovinyl) cyclopropenium ions.



Some destabilized carbocations, although not observed directly, could be generated *in situ* under Friedel-Crafts reaction conditions, for example, the destabilized diethyl malonyl cation (27).

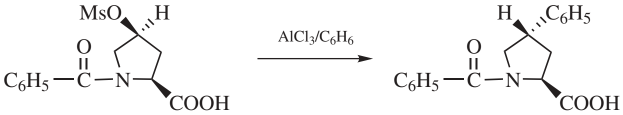


Highly unstable vinyl cations, generated *in situ* from vinyl triflates have also been arylated (the triflate group is replaced by the aromatics) to give vinyl aromatics under Friedel-Crafts conditions (28).

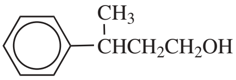
2.8. Alkylation with Alkanes. Superacids such as HF-SbF$_5$ abstract hydride ion from alkanes to form carbocations at low temperatures. The carbocations generated from C1–C5 alkanes, mixtures of alkanes and alkenes, as well as alkylbenzenes, alkylate benzene to give alkylated aromatics (29). Acid-catalyzed alkylation of benzene with cyclohexane has been brought about by using isobutane as the promoter. The principal products are cycloalkylbenzenes, substituted indanes, or tetralins, and C1–C6 alkylbenzenes (30). Ultrasound induced reactions of 2,2,4-trimethylpentane with benzene in the presence of catalysts such as CF_3SO_3H/SbF_5, $H[B(SO_3CF_3)_4]$, $AlBr_3$, HF/TaF_5, HF-NbF_5, and HF-TiF_4 proceed to give mainly *t*-butyl and di-*t*-butyl benzenes (31).

2.9. Stereoselective Alkylations. Benzene is stereoselectively alkylated with chiral 4-valerolactone in the presence of aluminum chloride with 50% net inversion of configuration (32). The stereoselectivity is explained by the coordination of the Lewis acid with the carbonyl oxygen of the lactone, resulting in the S_{N_2} type displacement at the C—O bond. Partial racemization of the substrate (incomplete inversion of configuration) results by internal return of the ion-pair complex with concomitant rotation of the C—C bond.

Both 2-methytetrahydrofuran [96-47-9] (32) and 3-chlorobutanoic acid [1951-12-8] (33) alkylate benzene with inversion of configuration. *N*-benzoyl-4-mesyloxy-L-proline reacts with benzene to give the corresponding 4-phenyl derivative with inversion of configuration (34).

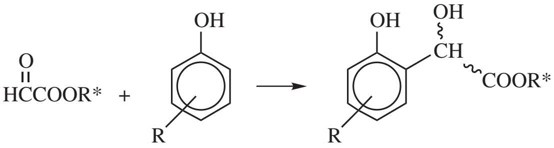


2-Methyloxetane [2167-39-7] alkylates benzene to give 3-phenyl-1-butanol:



with 20% inversion of configuration, using $AlCl_3$ or $TiCl_4$ as catalyst, whereas partial retention was observed with $SnCl_4$ (35). $AlCl_3$ catalyzed alkylation of benzene with enantiomerically pure 2-chloro-1-phenylpropane or 1-chloro-2-phenylpropane results in the formation of 1,2-diphenylpropane and 1,1-diphenylpropane, the former being formed with 45–100% retention of configuration. A π-phenyl assisted cation intermediate, with unsymmetrical bridging was proposed to account for the lack of racemization.

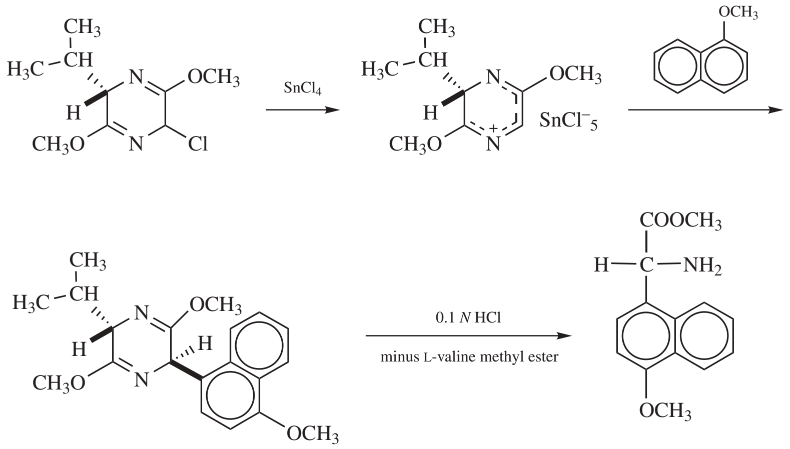
Chiral glyoxylates have been used to effect *ortho*-hydroxyalkylation of phenols via coordinative complexes. In this way, optically active 2-hydroxymandelic esters have been obtained with up to 94% diastereoselectivity (36).



R* = menthyl, etc; R = 3-*t*-butyl, 4-methoxy, etc

Stereoselectivity was also observed in the Friedel-Crafts reaction of optically active phenyloxirane with toluene and anisole. The product diarylethanol had an enantiomeric ratio of 60:40 (37).

Synthetic utility of stereoselective alkylations in natural product chemistry is exemplified by the preparation of optically active 2-arylglycine esters (38). Chirally specific α-amino acids with methoxyaryl groups attached to the α-carbon were prepared by reaction of the dimethyl ether of a chiral bis-lactam derivative with methoxy arenes. Using $SnCl_4$ as the Lewis acid, enantioselectivities ranging from 65 to 95% were obtained.



A combination of $C_{p2}ZrCl_2$–$AgClO_4$ (where C_p = cyclopentadienyl) effectively promotes the Friedel-Crafts coupling of glycosyl fluorides with aromatic compounds, such as trimethoxybenzene or methoxynaphthalenes. The derived C-aryl glycosides are potent antitumor agents (39).

Trimethylsilyl triflate–silver perchlorate (1:1) also catalyzes the highly stereoselective glycosylation of β-naphthol to provide predominantly the β-anomer.

Optically active 2-arylalkanoic acid esters have been prepared by the Friedel-Crafts alkylation of arenes with optically active α-sulfonyloxy esters (40). Friedel-Crafts alkylation of benzene with (*S*)-methyl 2-(chlorosulfonyloxy)- or 2-(mesyloxy)propionate proceeded with predominant inversion of configuration (<97%) to give (*S*)-methyl 2-phenylpropionate.

where X = Cl or CH_3

In view of the ready availability of optically pure lactic acid derivatives this reaction offers an attractive general method for the preparation of optically pure aromatic ester derivatives (41). Stereoselective alkylation (15–60% inversion) of benzene with optically active 1,2- 1,3- and 1,5-dihaloalkanes was also reported (42).

2.10. Haloalkylation. Haloalkyl groups can be introduced directly by processes similar to Friedel-Crafts alkylation into aromatic and, to some extent, aliphatic compounds. Because haloalkylations involve bi- or polyfunctional alkylating agents, they must be performed under conditions that promote the initial haloalkylation but not, to any substantial degree, subsequent further alkylations with the initially formed haloalkylated products.

The most frequently used haloalkylating agents are: aldehydes and hydrogen halides, haloalkyl ethers, haloalkyl sulfides, acetals and hydrogen halides, di- and polyhaloalkanes, haloalkenes, haloalcohols, haloalkyl sulfates, haloalkyl *p*-tosylates, and miscellaneous further haloalkyl esters. Haloalkylations include halomethylation, haloethylation, and miscellaneous higher haloalkylations. Under specific conditions, bis- and polyhaloalkylation can also be achieved.

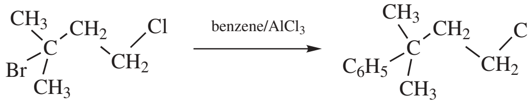
Haloalkylations are accompanied by further alkylation by the initially formed haloalkylated product, yielding diarylalkanes or cyclialkylated products, eg, benzene reacts with CCl_4 in the presence of $AlCl_3$ to give $C_6H_5CCl_3$ and $(C_6H_5)_2CCl_2$ (43). With dichloromethane, the initially formed benzyl chloride is further alkylated to diphenylmethane.

Acidic halide catalysts used in chloromethylation include (44) $ZnCl_2$, $ZnCl_2 + AlCl_3$, $SnCl_4$, $SnCl_2$, $AlCl_3$ +ketones, $AlCl_3$ + pyridine, $AlCl_3$ +tertiary amines, $AsCl_3$, $FeCl_3$, BF_3, $TiCl_4$, TiF_4, $BiCl_3$, $SbCl_3$, and $SbCl_5$. The most widely used protic acid catalysts are HCl, H_2SO_4, H_3PO_4, $H_2SnCl_6 \cdot 6H_2O$, $ClSO_3H + CH_3OH$, CH_3COOH, as well as benzene-, naphthalene-, and *p*-toluenesulfonic acids (44). Zinc chloride is probably the most frequently used catalyst. Its activity is sometimes increased by fusion with a small amount of aluminum chloride. In other instances, however, sufficient catalytic effect is obtained with a mineral acid alone.

Reactions have been brought about under heterogeneous conditions with an excess of aromatic compound serving as the solvent, and under homogeneous conditions, as in glacial acetic acid solution (45). Solvents used are diethyl ether, dioxane, dimethoxymethane, carbon tetrachloride, chloroform, ethylene chloride, perchloroethylene, nitrobenzene, ligroin (light petroleum distillate), and carbon disulfide.

Chloromethylation can be efficiently effected using chloromethyl methyl ether, in the presence of Lewis acids. However, due to its carcinogenic nature, extreme care should be exercised in its use (46). Alternatively, paraformaldehyde–HCl/$ZnCl_2$ can be used as the chloromethylating agent.

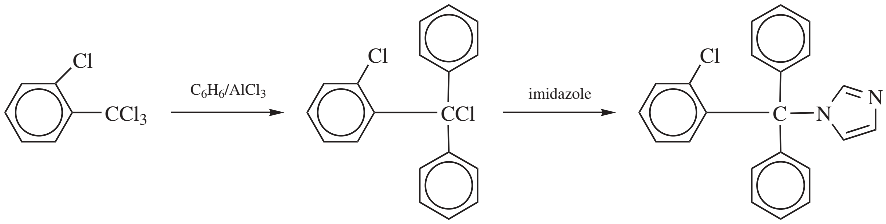
Selective monohaloalkylations were achieved when chlorobromoalkanes such as 1-chloro-3-bromo-3-methylbutane were used as haloalkylating agents (47). The bromine is replaced preferentially:



Fluorochloro, fluorobromo, and fluoroiodoalkanes react selectively with aromatics under boron trifluoride catalysis to provide chloro-, bromo- and iodoalkylated products (48). The higher reactivity of the C—F bond over C—Cl, C—Br, and C—I bonds under Lewis acid catalysis results in the observed products.

Alkenyl halides have also been used for haloalkylation reactions in the presence of protic acids (49).

The antifungal agent clotrimazole [23593-75-1] has been prepared by the Friedel-Crafts reaction of *o*-chlorobenzotrichloride [2136-89-2] and benzene in the presence of $AlCl_3$, followed by treatment with imidazole (50).

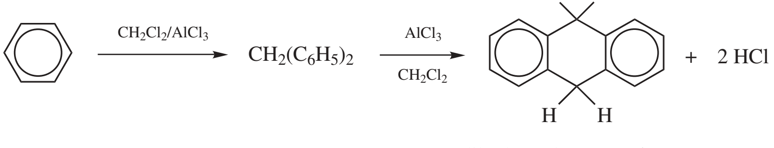


Fluoroalkylations are frequently performed indirectly using tandem reactions. Arenes react with sodium borohydride in trifluoroacetic acid to afford otherwise difficult to obtain 1,1,1-trifluoro-2,2-diarylethanes. Presumably sodium borohydride reacts initially with the trifluoroacetic acid to produce the trifluoroacetaldehyde or its equivalent, which rapidly undergoes Friedel-Crafts-type condensation to give an intermediate carbinol. The carbinol further alkylates benzene under the reaction conditions giving the observed product. The reaction with sterically crowded arenes such as mesitylene and durene proceeds only up to the carbinol stage (51). Although trichloroacetaldehyde is known to give similar products, the protic acid catalyzed Friedel-Crafts reactions of trifluoroacetaldehyde (fluoral) with arenes have not yet been reported. Trifluoroalkylated aromatics are also prepared using tris-[trifluoroacetoxy]borane in trifluoroacetic acid (52).

$$\mathrm{ArH} \xrightarrow[\text{2. NaOH/H}_2\text{O, 0°C}]{\text{1. CF}_3\text{COOH/NaBH}_4} \mathrm{ArCH(CF_3)OH} \xrightarrow{\mathrm{ArH}} \mathrm{ArCH(CF_3)Ar}$$

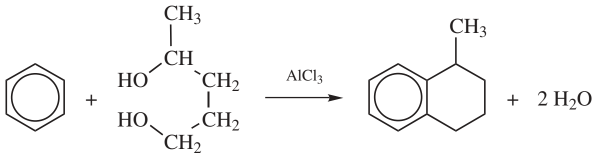
2.11. Cycloalkylation. Friedel-Crafts alkylation of aromatics with difunctional compounds leads partly to open-chain akylates but, if conditions are suitable, mainly to cyclic products (53). These compounds react at each end of the difunctional open chain, and thus attach a new ring to the aromatic nucleus. The difunctional alkylating agents first form monofunctional alkyl derivative with the aromatic compound which undergoes subsequent intramolecular alkylation forming the new fused ring. Extensive intermolecular reactions between the bifunctional alkylating agent and the aromatics can, however, also take place.

Ring formation readily occurs in the alkylation of aromatics with di- and polyhalides, eg, the reaction of di- and trihalomethanes with aromatics in the presence of aluminum chloride. In the reaction of dichloromethane and benzene, besides diarylmethanes, anthracene derivatives are also formed (54).



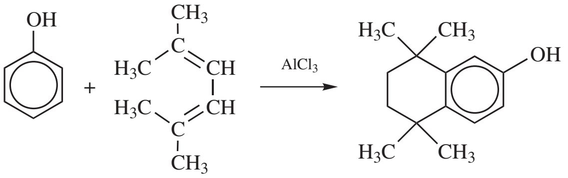
9,10-dihydroanthracene [*613-31-0*]

Cycloalkylation of aromatic compounds with 1,4- or 1,3-glycols in the presence of aluminum chloride leads to the formation of derivatives of tetrahydronaphthalene or indane, respectively (55).

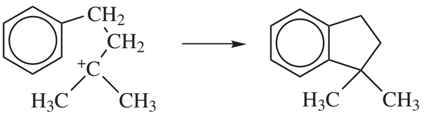


1-methyl-1,2,3,4-tetrahydronaphthalene

Dienes can also be used in Friedel-Crafts cycloalkylations. For example, treatment of phenol with 2,5-dimethyl-2,4 hexadiene gives 5,5,8,8-tetramethyl,6,7-dihydro-2-naphthol.



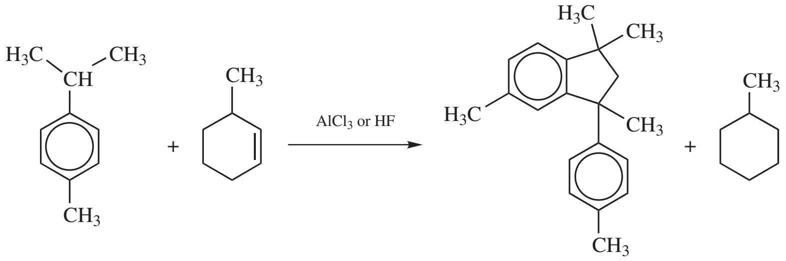
Intramolecular alkylation of haloalkylbenzenes is perhaps the simplest intramolecular counterpart of the classical Friedel-Crafts alkylation reaction. Primary, secondary, or tertiary phenylalkyl chlorides undergo ring closure. Compounds of the general formula $C_6H_5(CH_2)_nCl$ cyclize preferentially to give six-membered ring compounds. When a tertiary carbocation intermediate is involved, five-membered rings can be formed:



1,1-dimethylindane [*4912-92-9*]

Aromatic hydrocarbons with an unsaturated side chain undergo ring closure when heated with Lewis acids (56).

Alkylbenzenes containing an α-tertiary hydrogen, such as in isopropyl and *sec*-butyl side chains, rapidly transfer this hydrogen as a hydride ion producing an α-carbocation analogous to that in the protonation of styrene compounds. Subsequent alkylation of an olefin followed by ring closure produces indanes by much the same process. *p*-Cymene [99-87-6], on treatment with a branched olefin, such as methylcyclohexene, or trimethylethylene in the presence of an acid catalyst, yields 1,3,3,6-tetramethyl-1-*p*-tolylindane:



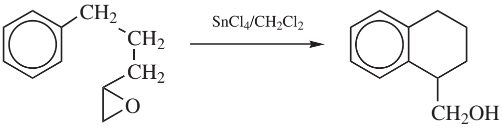
Synthetic and mechanistic studies of suitably substituted aryl and alkyl carbinols to give octahydrophenanthrenes have been reported (57).

Superacids such as HF-SbF$_5$ effect cycloalkylation of aryl alkyl ketones to give tetralone derivatives (58). Tandem intramolecular cycloalkylations can be achieved when functional groups are located in close proximity (59).

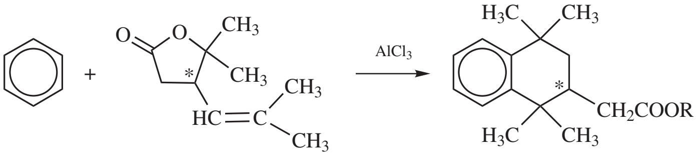
Friedel-Crafts metallocyclization of (halogenomethyl(aryl)phosphine) platinum(II) complexes in the presence of triphenylphosphine gives a cationic metallacyclic species (60).

Synthetic and mechanistic aspects of intramolecular cyclization in the tricyclic diterpenoid area have been studied in detail. In general, the presence of electron withdrawing groups such as carbonyl in the side chain retard the rates of cyclization (61).

Epoxide-opening intramolecular cyclizations, in light of their importance in natural product chemistry, have received much attention (62).



Double Friedel-Crafts alkylation of configurationally pure pyrocene (a substituted lactone) with aromatics results in the formation of cycloalkylation product with retention of configuration at the chiral center (63).



Tertiary 3- and 4-phenylalkanols undergo cycloalkylation readily with H$_2$SO$_4$. Primary and most secondary 3-phenylalkanols, however, do not, even at higher temperatures with H$_3$PO$_4$ (64). Cyclization of phenylalkyl alcohols to tetrahydronaphthalenes and indanes has been extensively investigated (65).

2.12. Arylation of Aromatic Compounds. In contrast to Friedel-Crafts alkylations, arylations of aromatics are not as well known, and usually require drastic conditions. They include: (*1*) dehydrogenating condensation (Scholl reaction); (*2*) arylation with aryl halides; and (*3*) arylation with diazonium halides.

The elimination of two ring hydrogens accompanied by the formation of an aryl–aryl bond under Friedel-Crafts conditions is known as the Scholl reaction (1). The dehydrogenating condensations can take place by either inter- or intramolecular pathways. Intermolecular Scholl reactions are numerous and include such reactions as formation of biphenyl from benzene, of perylene from naphthalene (through binaphthyl), of 2,2′-dipyridyl from pyridine, and the formation of high molecular weight polycondensed aromatics.

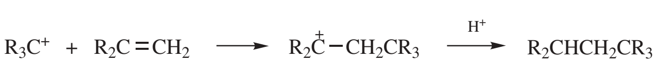
Aryl halides are rarely used as electrophilic arylating agents in Friedel-Crafts-type reactions. However, under suitable conditions, simple halobenzenes may be used as Friedel-Crafts arylating agents (66). Their decreasing order of reactivity is $F \gg Cl > Br$. Aromatic hydrocarbons are arylated with fluorobenzene in the presence of aluminum halides to the corresponding biphenyls. The directive effects are in agreement with electrophilic aromatic substitution.

In the investigation of the decomposition reaction of aryldiazonium tetrafluoroborates in nitrobenzene, it was found that in addition to fluorobenzene, 3,3′-dinitrobiphenyl was formed (67). An ionic type of arylation reaction seems to take place. Decomposition of aryldiazonium tetrafluoro-, tetrachloro-, and tetrabromoborates in aromatic solvents leads to electrophilic ring arylation (68).

2.13. Alkylation of Aliphatic Compounds. The first reported alkylation of branched-chain alkanes by ethylene, over aluminum chloride (69), made it possible to alkylate alkanes (except methane and ethane) with straight chain or branched alkenes.

$$\text{isobutane} \xrightarrow{\text{ethylene}} \text{hexanes} \xrightarrow{\text{ethylene}} \text{octanes} \xrightarrow{\text{ethylene}} \text{decanes}$$

The first industrial aliphatic alkylation process, the sulfuric acid catalyzed alkylation of branched alkanes with alkenes, was developed in 1938 (70). Because of its simplicity, low cost, the wide variety of raw materials, giving high octane alkylate, this process is still widely used. In the presence of 98.5–99.5% sulfuric acid, isobutane $(CH_3)_2CHCH_3$, isopentane $(CH_3)_2CHCH_2CH_3$, and isohexane $(CH_3)_2CHCH_2CH_2CH_3$ are easily alkylated by alkenes, producing alkylates with high octane numbers (see Alkylation; Catalysis). Anhydrous HF has replaced H_2SO_4 as the catalyst to a certain extent. The suggested reaction pathway is as follows:



$$R_2C{=}CH_2 \xrightarrow{H^+} R_2\overset{+}{C}{-}CH_3 \xrightarrow{R_3CH} R_2CHCH_3 + R_3C^+$$

$$R_3C^+ + R_2C{=}CH_2 \longrightarrow R_2\overset{+}{C}{-}CH_2CR_3 \xrightarrow{H^+} R_2CHCH_2CR_3$$

Products do not contain 2,2,3-trimethylbutane or 2,2,3,3-tetramethylbutane, which would be expected as the primary alkylation products of direct alkylation of isobutane with propylene and isobutylene, respectively. In fact, the process involves alkylation of the alkenes by the carbocations produced from the isoalkanes via intermolecular hydride abstraction.

On the other hand, under superacidic conditions, alkanes are readily alkylated via front-side σ-insertion by carbocationic alkylating agents. The direct alkylation of the tertiary C—H σ-bond of isobutylene with isobutane has been demonstrated (71).

The sterically unfavorable reaction of *tert*-butyl fluoroantimonate with isobutane gave a C_8 fraction, 2% of which was 2,2,3,3-tetramethylbutane:

$$(CH_3)_3C^+ + HC(CH_3)_3 \rightleftarrows (CH_3)_3CC(CH_3)_3 + H^+$$

When using HF:TaF_5 in a flow system for alkylation of excess ethane with ethylene (in a 9:1 molar ratio), only *n*-butane was obtained; isobutane was not detectable even by gas chromatography (72). Only direct σ-alkylation can account for these results. If the ethyl cation alkylated ethylene, the reaction would proceed through butyl cations, inevitably leading also to the formation of isobutane (through *t*-butyl cation).

Lower alkanes such as methane and ethane have been polycondensed in superacid solutions at 50°C, yielding higher liquid alkanes (73). The proposed mechanism for the oligocondensation of methane requires the involvement of protonated alkanes (pentacoordinated carbonium ions) and oxidative removal of hydrogen by the superacid system.

Natural gas, or methane itself can be converted into gasoline range hydrocarbons (C_4–C_6) by oxidative condensation over solid superacid catalysts (TaF_5/fluoridated Al_2O_3, SbF_5/fluorinated graphite, or TaF_5/AlF_3). Gasolines can be further converted into lower boiling (bp <196°C) hydrocarbons (diesel fuel-range hydrocarbons) by contact with a Friedel-Crafts catalyst, composed of high sodium ZSM-5 zeolite-bentonite at high temperatures (74).

The condensation of alkyl halides with olefinic hydrocarbons and haloolefins is catalyzed by Friedel-Crafts catalysts (75). The primary reaction consists of the addition of the alkyl group and the halogen atom to the double bond. In general, the reaction takes place more readily with tertiary than primary and secondary halides. Depending largely upon the particular reactants and the catalyst, the products are mainly alkyl halides containing quaternary carbon atoms, and are obtained in yields up to 75%. These compounds may further be dehydrohalogenated to the corresponding alkylated olefins and haloolefins.

2.14. Isomerization of Saturated Hydrocarbons. The ability of Friedel-Crafts-type superacids to protonate not only π-bonds but also the weaker σ-bonds of hydrocarbons at relatively low temperatures allows the isomerization of saturated hydrocarbons, which is of substantial practical importance (1). Straight-chain alkanes of the gasoline range (C_5–C_8 alkanes), have considerably lower octane numbers than their branched isomers. The isomerization of alkanes can be effected by catalysts such as $AlCl_3$, $AlBr_3$, HF–SbF_5, HF–TaF_5, HSO_3F–SbF_5, and the like. The stronger superacids allow the reaction at relatively low temperatures, which favor the branched alkanes (76). Processes for the isomerization of straight-chain alkanes in the gas phase over acid or zeolite (molecular-sieve) catalysts have been developed (see CATALYSIS; MOLECULAR SIEVES).

Isomerization of straight-chain hydrocarbons is of particular importance for lead-free gasoline. Addition of high octane aromatic hydrocarbons or olefins is questionable based on environmental considerations (77). An efficient octane enhancing additive is methyl *tert*-butyl ether (MTBE).

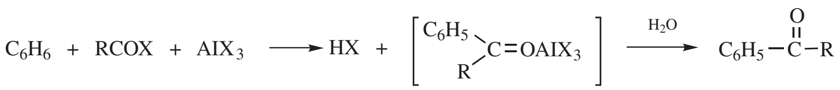
Friedel-Crafts acids such as $AlCl_3$, $AlBr_3$ (molten), or $AlBr_3$ (in CS_2 or low boiling hydrocarbon solvents) were found to be useful in the isomerization of cyclic hydrocarbons to cage hydrocarbons. For example, *endo*- or *exo*-trimethylenenorbornane, tetrahydrobinor-*S*, and heptacyclooctadecanes have been converted to adamantane, diamantane, and triamantane, respectively, in 10–60% yield (78). Use of superacidic catalysts, such as $B(OSO_2CF_3)_3$ and CF_3SO_3H–$B(OSO_2CF_3)_3$ lead to higher yields ranging from 70 to 90% (79).

3. Acylation

3.1. Acylation of Aromatic Compounds.

Ketone Synthesis. In the Friedel-Crafts ketone synthesis, an acyl group is introduced into the aromatic nucleus by an acylating agent such as an acyl halide, acid anhydride, ester, or the acid itself. Ketenes, amides, and nitriles also may be used; aluminum chloride and boron trifluoride are the most common catalysts (see KETONES).

Reaction of the aromatic (eg, C_6H_6), acyl halide (RCOX), and aluminum halide (AlX_3) liberates hydrogen halide and produces a complex of aromatic ketone and aluminum halide from which the ketone is liberated by hydrolysis:



$$C_6H_6 + RCOX + AlX_3 \longrightarrow HX + \left[(C_6H_5)(R)C{=}OAlX_3 \right] \xrightarrow{H_2O} C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}R$$

Apparently a molar equivalent of catalyst ($AlCl_3$) combines with the acyl halide, giving a 1:1 addition compound, which then acts as the active acylating agent. Reaction with aromatics gives the $AlCl_3$ complex of the product ketone liberating HX:

$$RCOX + AlX_3 \longrightarrow RCOX \cdot AlX_3 \rightleftharpoons RCO^+AlX^-{}_4$$

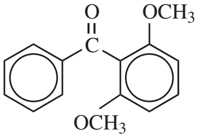
$$ArH + RCO^+\ AlX^-{}_4 \longrightarrow ArCOR \cdot AlX_3 + HX$$

Evidence supporting the formation of 1:1 addition compounds is substantiated by the actual isolation of stable acyl halide–Lewis acid complexes.

If the catalyst gets firmly attached to the resulting ketone, it is no longer able to activate more acyl halide (80). However, halogen exchange between acyl and aluminum halides continues in the presence of excess ketone. Apparently, the presence of ketone does not prevent formation of acyl cation but lowers its efficiency as an acylating agent. Similarly, the ability of certain solvents such as nitrobenzene, nitromethane, and carbon disulfide, to modify Friedel-Crafts acylation reactions is related to their ability to complex acyl cations, thus reducing their electron deficiency.

A further consequence of association of acylating agents with basic compounds is an increase in the bulk of the reagent, and greater resistance to attack at the more sterically hindered positions of aromatic compounds. Thus acylation of chrysene and phenanthrene in nitrobenzene or in carbon disulfide occurs to a considerable extent in an outer ring, whereas acylation of naphthalene leads to extensive reaction at the less reactive but sterically less hindered 2-position.

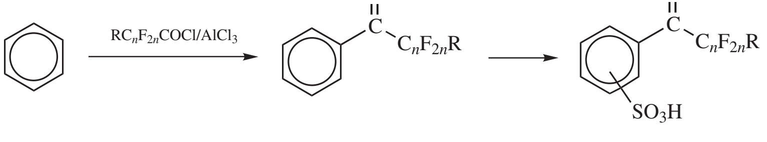
Friedel-Crafts acylation of aromatics is of considerable practical value owing to the importance of aryl ketones and aldehydes. Acylating agents in general are more reactive than alkylating agents, and the reaction of acyl halides with aromatic compounds in the presence of a Friedel-Crafts catalyst proceed readily. These reactions are also successful with aromatic amino derivatives, although as a general rule, electronegative groups have an inhibiting effect. Usually, it is difficult to introduce more than one acyl group into an aromatic ring, although some diacylation products are reported in the literature. A high yield of diacetylmesitylene was obtained when mesitylene was acetylated with a sixfold excess of catalyst and using the Elbs method (81). In another study (82), 63% conversion to the diacylated product was obtained in the acetylation of fluoroanthrene. Reaction of benzene with 2,6-dimethoxybenzoyl chloride gives products indicating acylation of the ring of the acyl chloride as well as acylation of benzene, yielding 2,6-dimethoxybenzophenone [25855-75-8] (83).



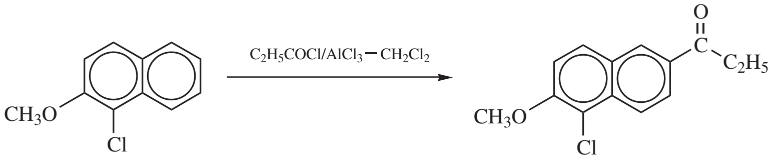
In the Friedel-Crafts acylation of ortho–para directing aromatic compounds para derivatives are formed, in most cases, preferentially over the ortho isomers. The reason for this behavior was long attributed to steric factors, although exceptions were known (84). In a systematic study of the effect of substituents in acylating agents on the selectivity of Friedel-Crafts acylation (85), the $AlCl_3$-catalyzed benzoylation of toluene with benzoyl chloride gave 8% 2- and 91% 4-methylbenzophenone. In contrast, acylation with 2,6-dinitrobenzoyl chloride gave 42% ortho isomer and 55% para isomer. These results show that the relative reactivity of the electrophilic acylating agents affects the isomer distribution (86).

1-Phenylnorbornane is benzoylated faster than isopropylbenzene or toluene despite the bulkiness of the norbornyl group probably because of hyperconjugation (87). Hyperconjugation of the C—C bond is at least as or more important as that of the C—H bond since 1-phenylnorbornane has no α-hydrogen atom.

Industrial Applications. Perfluoroacylbenzene sulfonates, used as additives in fire-extinguishing compounds and galvanizing baths have been prepared (88). Perfluoroacylbenzenesulfonate salts prepared by Friedel-Crafts reaction of perfluoroacyl halides and benzene, and subsequent sulfonation have been used as surfactants (89).

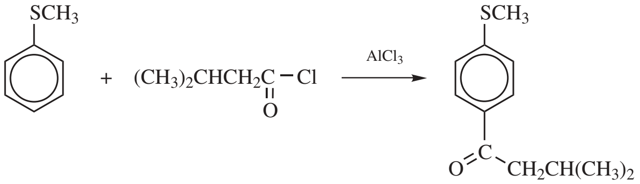


1-(5-Chloro-6-methoxy-2-naphthyl)-1-propanone has been prepared by Friedel-Crafts reaction of propanoyl chloride with 1-chloro-2-methoxy naphthalene, and is used as an intermediate for the antiinflammatory/analgesic naproxen [22204-53-1] (90) (see ANALGESICS, ANTIPYRETICS, AND ANTIINFLAMMATORY AGENTS).

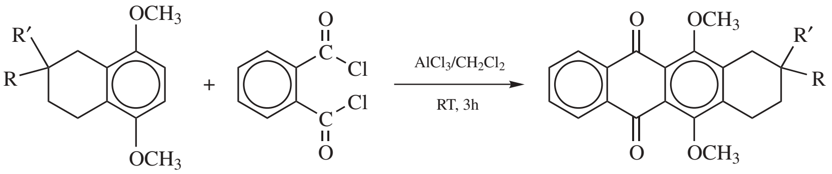


Trihaloacyl aromatics have been prepared by Friedel-Crafts acylation of aromatics with CX_3COCl (X = Cl, Br) in the presence of $AlCl_3$. They are used as monomers in the preparation of polycarbonates, polyesters, polyamides, polyketones, and polyurethanes (91).

Friedel-Crafts acylation of phenyl methyl thioether with 3-methylbutanoyl chloride gives 4-acetylated thioether, which is used as an intermediate for antihypertensive drugs (92).

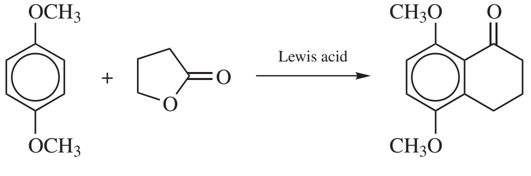


Dihydroxytetrahydronapthacenedione derivatives, used as intermediates for the anthracycline antibiotics have been prepared by Friedel-Crafts reaction of tetralin derivatives with orthophthaloyl chloride [88-95-9] in high yields (93).



Friedel-Crafts acylation of 3,3-dimethyl-2-indolinone by succinic anhydride gives 3,3-dimethyl-5-(3-carboxypropionyl)-2-indoline, which is used as an intermediate in the preparation of inotropic agents for treatment of heart failure (94). Antibacterial phlorophenone derivatives have been prepared by Friedel-Crafts acylation with propanoyl chloride (95).

Friedel-Crafts reaction of *p*-methoxybenzene with γ-butyrolactone gives the dimethoxytetralone, which serves as an intermediate for anthracyclinones, such as daunomycinone [21794-55-8] (96).



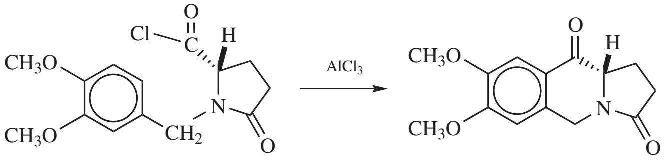
1-Naphthylacetic acid derivatives, showing antiinflammatory, analgesic, and antipyretic activities are prepared by Friedel-Crafts acylation of methyl 1-naphthyl acetate at the 4 position with $(CH_3)_2CHCOCl$ followed by Clemmensen reduction (97).

Friedel-Crafts acetylation of cyclohexylbenzene gave 4-cyclohexylacetophenone which was used as an intermediate for the preparation of 2,4-dioxo-4-substituted-1-butanoic acid derivatives useful in treating urinary tract calcium oxalate lithiasis (98).

Acyl fluoride–Lewis acid complexes are stable acylium (oxocarbonium) salts that can be used advantageously in a modification of the Perrier synthesis (99). The reaction of acyl chlorides or bromides with anhydrous complex fluoro-silver salts also leads to the preparation of acylium salts that are highly reactive acylating agents. Because these metathetic reactions are brought about in acid-free media (the only acid present is by-product conjugate acid formed in the substitution reaction with aromatics), they are applicable to systems otherwise sensitive to Lewis or Brønsted acid catalysts.

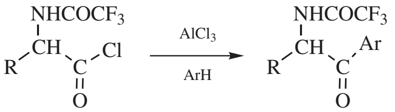
$$\mathrm{RCOCl} + \mathrm{AgSbF_6} \longrightarrow \mathrm{RCO^+SbF^-{}_6} + \mathrm{AgCl}$$

Stereoselective Acylations. Intramolecular Friedel-Crafts acylation reaction of *N*-aralkyl α-amino acid derivatives gives cyclic ketones with high enantioselectivity (100). This methodology has been used for the enantiospecific syntheses of tylophorine [482-20-2] and cryptopleurine [87302-53-2], the principal representatives of phenanthroindolizidine and phenanthroquinolizidine alkaloids (qv) (101).

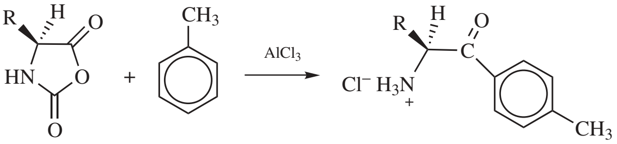


The reaction can be used in the large-scale production of the optically active amino acid derivatives. The chirality of the α-carbon is substantially retained and resolution of the product is avoided.

N-Trifluoroacetylamino acid chlorides also undergo intermolecular Friedel-Crafts acylation reaction with complete preservation of chirality to provide similar natural products (102,103).



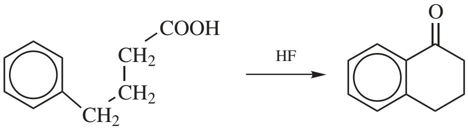
Similarly, *N*-carboxy-α-amino acid anhydrides react with aromatics such as toluene, xylenes, and mesitylene to give α-amino acylated products in moderate yields with almost complete retention of configuration of the α-amino acid.



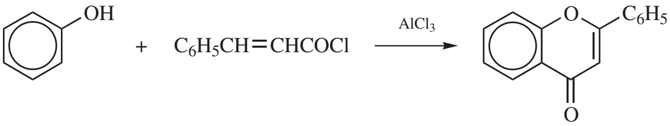
The *N*-carboxyl group is lost during the reaction, and no additional deprotection step is required (104). Benzene reacts with *N*-carboxyglycine anhydride to give aminomethyl phenyl ketone; however, it does not react with other *N*-carboxy-α-amino acid anhydrides (105).

Cycloacylation. Cyclic ketones can be prepared by intramolecular Friedel-Crafts acylation of an aromatic ring that has an acyl halide group in an attached side chain (1). The method is used in the preparation of hydrindones, tetralones, chromones, xanthones, etc. Cyclization of ketoacyl chlorides leading to the formation of coumarandiones, chromandiones, indandiones, and anthraquinones are further examples of intramolecular cycloacylations; five- and six-membered ring ketones are generally obtained in good yield by this method. Polyphosphoric acid (PPA) is often employed as a catalyst for cycloacylations.

In an alternative procedure the acids themselves undergo cyclization catalyzed by hydrogen fluoride. γ-Phenylbutyric acid [36541-31-8] can be cyclized to α-tetralone [29059-07-2] by this method:



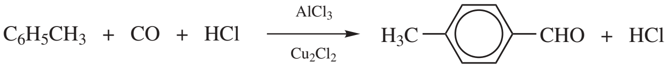
Cycloacylations readily take place in intermolecular acylations involving bifunctional acylating agents. Both functional groups may be acyl (as in the case of α,ω-diacyl halides) or one may be an alkylating group (as in unsaturated acyl halides or certain haloacyl halides) (18).



Polystyrene can be cross-linked by its acylation with bifunctional acylating agents such as adipoyl, sebacoyl, or malonyl chlorides in the presence of $AlCl_3$ in CS_2 solution at 0°C (106).

Aldehyde Synthesis. Formylation would be expected to take place when formyl chloride or formic anhydride reacts with an aromatic compound in the presence of aluminum chloride or other Friedel-Crafts catalysts. However, the acid chloride and anhydride of formic acid are both too unstable to be of preparative interest.

In the presence of aluminum chloride and a small amount of cuprous halide, a mixture of hydrogen chloride and carbon monoxide serves as a formylating agent of aromatics (Gattermann-Koch reaction) (107):



Intermediate formation of formyl chloride is not necessary since the actual alkylating agent, HCO^+, can be produced by protonation of carbon monoxide or its complexes. However, it is difficult to obtain an equimolar mixture of anhydrous hydrogen chloride and carbon monoxide. Suitable laboratory preparations involve the reaction of chlorosulfonic acid with formic acid or the reaction of benzoyl chloride with formic acid:

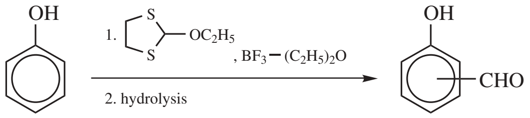
$$\mathrm{HCOOH} + \mathrm{ClSO_3H} \longrightarrow \mathrm{H_2SO_4} + \mathrm{CO} + \mathrm{HCl}$$

$$\mathrm{HCOOH} + \mathrm{C_6H_5COCl} \longrightarrow \mathrm{C_6H_5COOH} + \mathrm{CO} + \mathrm{HCl}$$

The Gattermann-Koch synthesis is suitable for the preparation of simple aromatic aldehydes from benzene and its substituted derivatives, as well as from polycyclic aromatics. The para isomers are produced preferentially. Aromatics with meta-directing substituents cannot be formylated (108).

Formylation of aromatics using superacid catalyst systems such as $HF\text{-}BF_3$ (109), $HF\text{-}SbF_5$ (110), $HF\text{-}CF_3SO_3H\text{-}BF_3$ (111), and CF_3SO_3H (112), and $FSO_3H\text{–}SbF_5$ (113) has been achieved in good yields. Formylation of alkylbenzenes using $SbF_5\text{–}FSO_3H$ resulted in the formation of alkylbenzaldehydes and formylalkylbenzenesulfonyl fluorides. The composition of the products was dependent on the acidity of the medium. At high acidities, the formyl derivative was the primary product, whereas lowering of the acidity by decreasing the amount of SbF_5 resulted in sulfonyl compounds.

Aromatics containing electron releasing groups such as phenols, dimethylaminobenzene and indole are formylated by 2-ethoxy-1,3-dithiolane in the presence of boron trifluoroetherate, followed by hydrolysis (114). The preformed dithiolanium tetrafluoroborate also undergoes Friedel-Crafts reaction with aromatics such as dimethylaminobenzene and indole (115), and was used to generate dithiolanium derivatives (formyl precursors) from the enoltrimethylsilyl ether derivatives (116).



Whereas the above reactions are applicable to activated aromatics, deactivated aromatics can be formylated by reaction with hexamethylenetetramine in strong acids such as 75% polyphosphoric acid, methanesulfonic acid, or trifluoroacetic acid to give salicylaldehyde derivatives (117). Formyl fluoride (HCOF) has also been used as formylating agent in the Friedel-Crafts reaction of aromatics (118). Formyl fluoride [1493-02-3] in the presence of BF_3 was found to be an efficient electrophilic formylating agent, giving 53% para-, 43% ortho- and 3.5% meta-tolualdehydes upon formylation of toluene (110).

Attempts to use acetic-formic anhydride with Friedel-Crafts catalysts resulted only in acetylation. However, using anhydrous HF as a catalyst, a small amount of aldehyde is also formed in accordance with the fact that acetic–formic anhydride gives both acetyl and formyl fluoride with HF. By continuous removal of the low boiling HCOF, the reaction can be shifted to the formation of this compound (118).

In the presence of strongly acidic media, such as triflic acid, hydrogen cyanide or trimethylsilyl cyanide formylates aromatics such as benzene. Diprotonotated nitriles were proposed as the active electrophilic species in these reactions (119).

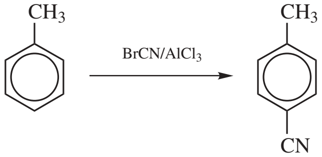
Friedel-Crafts acylation using nitriles (other than HCN) and HCl is an extension of the Gattermann reaction, and is called the Houben-Hoesch reaction (120–122). These reactions give ketones and are usually applicable to only activated aromatics, such as phenols and phenolic ethers. The protonated nitrile, ie, the nitrilium ion, acts as the electrophilic species in these reactions. Nonactivated benzene can also be acylated with the nitriles under superacidic conditions 95% trifluoromethanesulfonic acid containing 5% SbF_5 ($H_0 > -18$) (119). A dicationic diprotonated nitrile intermediate was suggested for these reactions, based on the fact that the reactions do not proceed under less acidic conditions. The significance of dicationic superelectrophiles in Friedel-Crafts reactions has been discussed (123,124).

Aromatic and heterocyclic compounds are formylated by reaction with dialkyl- or alkylarylformamides in the presence of phosphorus oxychloride or phosgene (Vilsmeier aldehyde synthesis) (125). The Vilsmeier reaction is a Friedel-Crafts type formylation (126), since the intermediate cation formed by the interaction of phosphorus oxychloride with formamide is a typical electrophilic reagent. Ionic addition compounds of formamide with phosgene or phosphorus oxychloride are also known (127).

$$\mathrm{ArH} + \mathrm{R_2NCHO} \xrightarrow{\mathrm{POCl_3}} \mathrm{ArCHO} + \mathrm{R_2NH}$$

Aromatic compounds are formylated also by dichloromethyl methyl ether or trialkyl orthoformates (128).

Nitrile Synthesis. Cyanogen bromide [506-68-3] condenses with toluene in the presence of aluminum chloride to give *p*-tolunitrile (129).



An alternative method consists of the reaction of trichloroacetonitrile [545-06-2] with a hydrocarbon and $AlCl_3$. A ketimine is formed which is hydrolyzed by treatment with potassium hydroxide into the nitrile and chloroform. The reaction proceeds with aromatics such as toluene and phenols (130).

Tertiary alkyl chlorides have been converted to the tertiary nitriles with trimethylsilyl nitrile in dichloromethane in the presence of $SnCl_4$ (131). The reaction was applied to the synthesis of several bridgehead nitriles, such as 1-adamantyl and 1-diamantyl nitriles from the corresponding chloro or bromo derivatives using $SnCl_4$ or $AlBr_3$ catalysts (132).

Preparation of Arylcarboxylic Acids and Derivatives. The general Friedel-Crafts acylation principle can be successfully applied to the preparation of aromatic carboxylic acids. Carbonyl halides (phosgene, carbonyl chloride fluoride, or carbonyl fluoride) [353-50-4] are diacyl halides of carbonic acid. Phosgene [75-44-5] or oxalyl chloride [79-37-8] react with aromatic hydrocarbons to give aroyl chlorides that yield acids on hydrolysis (133):

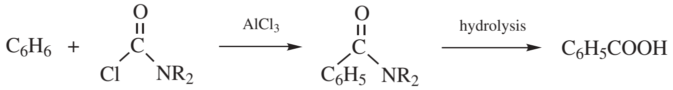
$$C_6H_6 + COCl_2 \xrightarrow[-HCl]{AlCl_3} C_6H_5COCl \xrightarrow{H_2O} C_6H_5COOH$$

However, excess aromatics can give the corresponding ketones:

$$C_6H_5COCl \xrightarrow[-HCl]{C_6H_6/AlCl_3} C_6H_5COC_6H_5$$

Carbon disulfide as solvent favors the formation of the acid since the intermediate complex formed, $C_6H_5COCl{\cdot}AlCl_3$, is insoluble in it and by precipitation avoids secondary ketone formation.

Ketone formation can also be avoided if one of the functional acyl halogens in phosgene is blocked. Carbamyl chlorides, readily obtained by the reaction of phosgene with ammonia or amines, are suitable reagents for the preparation of amides in direct Friedel-Crafts acylation of aromatics. The resulting amides can be hydrolyzed to the corresponding acids (134):



$$C_6H_6 + Cl{-}C({=}O){-}NR_2 \xrightarrow{AlCl_3} C_6H_5{-}C({=}O){-}NR_2 \xrightarrow{\text{hydrolysis}} C_6H_5COOH$$

The practical application of this reaction has been demonstrated in the preparation of terephthalic acid from toluene, in which case oxidation follows hydrolysis (135). The reaction also proceeds well with substituted carbamyl chlorides such as $C_6H_5(C_2H_5)NCOCl$.

Amides result from the reaction of aromatic hydrocarbons with isocyanates, such as phenyl isocyanate [103-71-9], in the presence of aluminum chloride. Phenyl isothiocyanate [103-72-0] similarly gives thioanilides (136).

$$C_6H_5NCO + C_6H_6 \xrightarrow{AlCl_3} C_6H_6NHCOC_6H_5$$

In these reactions the active acylating agent is the carbamyl chloride, formed by the reaction of the isocyanate with hydrogen chloride (137):

$$C_6H_5NCO + HCl \longrightarrow C_6H_5NHCOCl$$

Carbon dioxide can be considered the acid anhydride of carbonic acid. Accordingly, it reacts with benzene, albeit in low yield, to give benzoic acid and benzophenone in the presence of aluminum chloride.

With more reactive substances, zinc or ferric chlorides may be substituted as catalysts (138). More elevated temperatures and high pressure are, however, generally needed, and only very reactive substrates (such as phenols) react readily.

3.2. Analogues of Acylation Reactions.

Sulfonylation. Under Friedel-Crafts reaction conditions, sulfonyl halides and sulfonic acid anhydrides sulfonylate aromatics (139), a reaction that can be considered the analogue of the related acylation with acyl halides and anhydrides. The products are sulfones. Sulfonyl chlorides are the most frequently used reagents, although the bromides and fluorides also react:

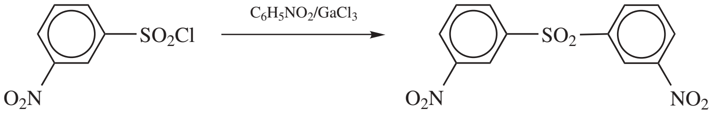
$$C_6H_6 + RSO_2Cl \xrightarrow{AlCl_3} C_6H_5SO_2R + HCl$$

Methanesulfonic and benzenesulfonic anhydrides are the most frequently used anhydrides in Friedel-Crafts sulfonylation reactions:

$$C_6H_6 + (CH_3SO_2)_2O \longrightarrow C_6H_5SO_2CH_3 + CH_3SO_3H$$

Benzenesulfonic anhydride has been claimed to be superior to benzenesulfonyl chloride (140). Catalysts used besides aluminum chloride are ferric chloride, antimony pentachloride, aluminum bromide, and boron trifluoride (141).

Sulfonation. The general Friedel-Crafts acylation principle can be applied to sulfonation with halides and anhydrides of sulfuric acid (halosulfuric acids, sulfur trioxide). Aluminum chloride and boron trifluoride are effective catalysts in certain sulfonations with halosulfuric acids. In general, sulfonations by sulfuric acid or oleum should also be considered within the scope of Friedel-Crafts acylations, providing both sulfonating agent and catalyst. However, strong Lewis acid catalysts such as $GaCl_3$ are required for the sulfonation of deactivated aromatics, such as nitrobenzene (142).



2,4,5,4′-tetrachlorodiphenyl sulfone [116-29-0], used as a pesticide has been prepared by the Friedel-Crafts sulfonation of 2,4,5-trichlorobenzenesulfonyl chloride with chlorobenzene (143).

Sulfonation of aromatic hydrocarbons with sulfuric acid is catalyzed by hydrogen fluoride or, at lower temperatures, by boron trifluoride (144). The products obtained are more uniform and considerably less sulfuric acid is needed, probably because BF_3 forms complexes with the water formed in the reaction, and thus prevents dilution of the sulfuric acid.

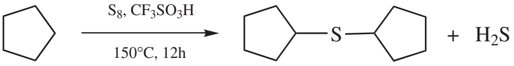
The migration of alkyl or halogen atoms during the sulfonation of polyalkyl (polyhalo) benzenes containing at least four substituents is known as the Jacobsen rearrangement (145). Thus 2,3,5,6-tetramethylbenzenesulfonic acid is rearranged chiefly to 2,3,4,5-tetramethylbenzenesulfonic acid (see SULFUR COMPOUNDS).

Sulfination. Benzene and its homologues react with SO_2 in the presence of $AlCl_3$ and HCl to form sulfinic acids (146)

$$C_6H_6 + SO_2 \xrightarrow[HCl]{AlCl_3} C_6H_5SO_2H$$

Sulfuration. Hydrocarbons, such as cyclohexane and *n*-pentane have been converted to dicyclohexyl and dipentyl sulfides by monoclinic sulfur in the presence of $AlCl_3$, $GaCl_3$, or $FeCl_3$. These reactions are accelerated by the addition of HCl or HBr and give a mixture of products in many instances (147). Alkylbenzenes also react with sulfur in the presence of $AlCl_3$ to give a mixture of sulfurated products consisting mainly of diaryl sulfides, 1,2-dithiol-3-thiones, and substituted thiophenes (148).

Elemental sulfur reacts with alkanes such as cyclopentane in the presence of superacidic trifluoromethanesulfonic acid to give symmetrical dialkyl sulfides in moderate yields.



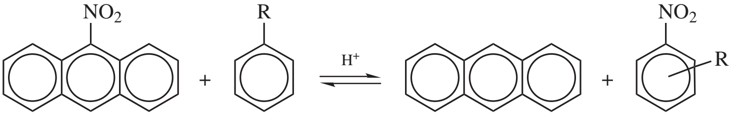
These reactions involve the intermediate formation of thiols, followed by condensation to the sulfides. The observation of isomerized products in suitable cases indicates the intermediate formation of carbocations, either by protolysis of alkanes by the superacid or reversible ionization of the thiol products (149).

Nitration. The general Friedel-Crafts acylation principle can also be applied to nitration involving nitryl halides and dinitrogen pentoxide (the halides and anhydride of nitric acid). In a more general sense, nitration with nitric acid catalyzed by proton acids (H_2SO_4, $HClO_4$, HF, etc) or by Lewis halides (BF_3, $AlCl_3$, etc) should also be considered as Friedel-Crafts-type reactions in analogy to the ketone syntheses where carboxylic acids are used as acylating agents. Friedel-Crafts nitration using nitryl chloride, NO_2Cl, with aluminum chloride as catalyst has been reported (150). Anhydrous silver tetrafluoroborate is also a suitable methatetic cation-forming agent in these reactions (151).

Dinitrogen tetroxide is an effective Friedel-Crafts nitrating agent (152) for aromatics in the presence of aluminum chloride, ferric chloride, or sulfuric acid (153). Dinitrogen pentoxide is a powerful nitrating agent, even in the absence of catalysts, preferably in sulfuric acid solution (154). Solid dinitrogen pentoxide is known to be the nitronium nitrate, $(NO_2)^+(NO_3)^-$. The use of BF_3 as catalyst has been reported (155).

Stable nitronium salts such as $(NO_2)^+(BF_4)^-$, $(NO_2)^+(AsF_6)^-$, $(NO^+{}_2)_2$ $(SiF_6^2)^-$, $(NO_2)^+(HS_2O_7)^-$, etc, are extremely powerful Friedel-Crafts nitrating agents for aromatics (156). Nitronium tetrafluoroborate is easily obtained from N_2O_5, HF, and BF_3, or from nitric acid, HF, and BF_3 (157).

Nitrations can be performed in homogeneous media, using tetramethylene sulfone or nitromethane (nitroethane) as solvent. A large variety of aromatic compounds have been nitrated with nitronium salts in excellent yields in nonaqueous media. Sensitive compounds, otherwise easily hydrolyzed or oxidized by nitric acid, can be nitrated without secondary effects. Nitration of aromatic compounds is considered an irreversible reaction. However, the reversibility of the reaction has been demonstrated in some cases, eg, 9-nitroanthracene, as well as pentamethylnitrobenzene transnitrate benzene, toluene, and mesitylene in the presence of superacids (158) (see NITRATION).



Perchlorylation. The stability of perchloryl fluoride [7616-94-6], $FClO_3$, makes possible perchlorylation of aromatics, a reaction closely related to the Friedel-Crafts acylation (159):

$$C_6H_6 + FClO_3 \xrightarrow{AlCl_3} C_6H_5ClO_3 + HF$$

Aluminum bromide and chloride are equally active catalysts, whereas boron trifluoride is considerably less active probably because of its limited solubility in aromatic hydrocarbons. The perchloryl aromatics are interesting compounds but must be handled with care because of their explosive nature and sensitivity to mechanical shock and local overheating.

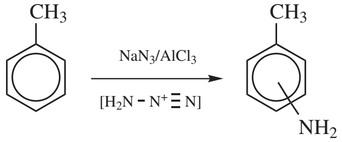
Halogenation. The halogenation of a wide variety of aromatic compounds proceeds readily in the presence of ferric chloride, aluminum chloride, and related Friedel-Crafts catalysts. Halogenating agents used are elementary halogens (chlorine, bromine, or iodine), and interhalogens (such as iodine monochloride and bromine monochloride). Although iodination can also be achieved, oxidative conditions must be provided in order to remove the HI formed, which otherwise tends to reduce the ring-iodinated compounds (160). The extent of halogenation is regulated by the amount of halogenating agent used and by reaction conditions. Alkylated benzenes, phenols, phenol ethers, and polynuclear hydrocarbons undergo ring halogenation with ease.

Bromination can be conveniently effected by transfer of bromine from one nucleus to another. As the Friedel-Crafts isomerization of bromoaromatic compounds generally takes place through an intermolecular mechanism, the migrating bromine atom serves as a source of positive bromine, thus effecting ring brominations (161,162). 2,4,6-Tribromophenol, for example, has been prepared by bromination of phenol with dibromobenzene.

Hydroxylation. The direct synthesis of phenol from benzene is of interest since phenol is widely used in industry and benzene is a relatively cheap starting material for phenol. Electrophilic hydroxylation of benzene with H_2O_2 or peracids, catalyzed by $AlCl_3$, BF_3, etc, usually results in mixtures containing also polyhydroxybenzenes and oxidized products. Using superacidic systems selective monohydroxylation is, however, possible. The phenyloxonium ion formed by protonation of the hydroxy group during the reaction is unreactive towards electrophiles, resulting in no further hydroxylation.

H_2O_2 in the presence of HF/BF_3 acts as an effective and economical reagent for aromatic hydroxylation (163). Hydroxylations of phenols and amines in similar high acidity media are very effective (163). Xylenes were hydroxylated by bis(trimethylsilyl) peroxide and $AlCl_3$ in poor yields (164). Bis(trimethylsilyl) peroxide $(CH_3)_3SiOOSi(CH_3)_3$ can be used with triflic acid (CF_3SO_3H) and acts as an effective hydroxylating agent of aromatics such as toluene, mesitylene and naphthalene (165). Sodium perborate (a safe and inexpensive commercial chemical) can be used in conjunction with the triflic acid to hydroxylate aromatics (166).

Amination. Direct amination of aromatics can be achieved through the use of $NH_2OH \cdot HCl$, or NH_2OSO_3H in the presence of aluminum chloride or chloramine (NH_2Cl) (167). Usually more than two equivalents of Friedel-Crafts catalysts are employed. The catalysts coordinate with the reagent assisting in the increased polarization of the N—O bond. Although these reactions are electrophilic in nature, it is unlikely that free $NH^+{}_2$ is involved. Aromatics have been aminated with *in situ* prepared amino diazonium ion through the reaction of sodium azide and aluminum chloride (168).

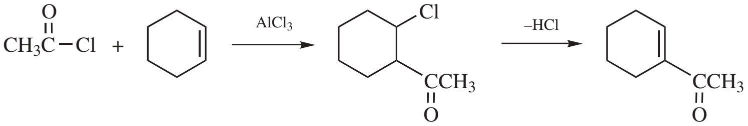


Subsequently it was found that trimethylsilyl azide in triflic acid is a more efficient and improved reagent for aminations (169). Amination of toluene in the presence of trichloramine–$AlCl_3$ proceeds predominantly at the *m*-position.

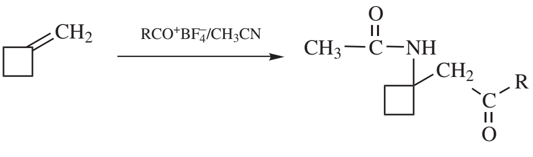
3.3. Acylation of Aliphatic Compounds.

Similar to alkylation, not only aromatic but also aliphatic and cycloaliphatic compounds undergo Friedel-Crafts acylation reactions.

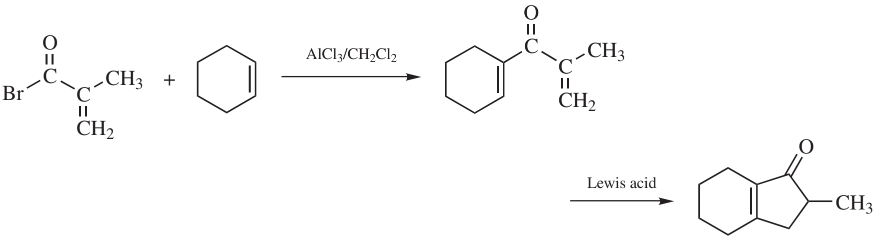
Olefins and cycloolefins give unsaturated ketones with acyl halides (the Nenitzescu reaction) (170). Saturated chloroketones are formed as intermediates followed by elimination of HCl. Similar products may be obtained by using acid anhydrides. 1-Methylcyclopentene on acylation with acetyl bromide in the presence of $AlCl_3$ gives 1,3-diacetyl-2-methylcyclopentene and 1-acetyl-2-methylcyclopentene in a ratio of 40:60 (171).



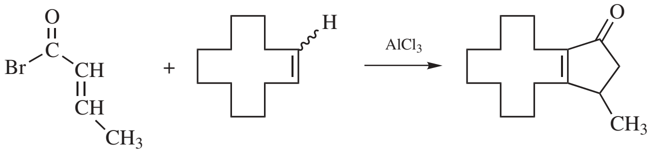
The β-halo ketone intermediates formed in the foregoing reactions arise from the capture of carbocationic intermediates by halide of the gegenions. In some cases, solvents such as acetonitrile can act as the competing nucleophilic species. For example, β-amido ketones could be obtained by the acylation of alkenes in acetonitrile (172).



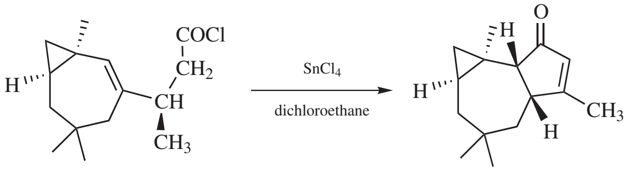
Using α,β-unsaturated acyl halides, alkenes are acylated to give α,β,α′,β′-unsaturated ketones, which undergo spontaneous intramolecular Nazarov cyclizations to cyclopentenones, important precursors of natural products (173).



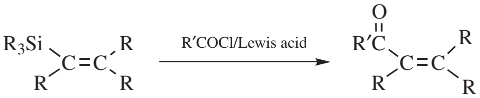
Cyclododecene (cis and trans) was similarly transformed to the cyclic enone, which is an important intermediate in the preparation of perfumary products, such as muscone [541-91-3].



Intramolecular Friedel-Crafts acylations of olefins also give cyclic α,β-unsaturated cyclic ketones. Cyclopropane fused bicyclo[5.3.0]octenones, thus obtained, were used in the preparation of the marine sesquiterpenes, africanol [53823-07-7] and dactylol [58542-75-9] (174).

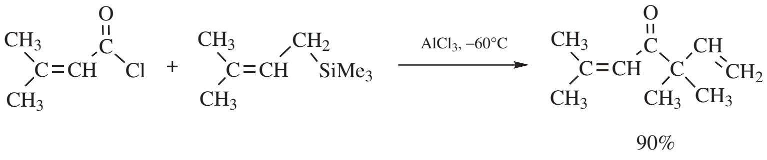


The rather harsh conditions that are used in the acylation of olefins can be avoided in suitable cases by the incorporation of silyl groups. Thus, acylations of trialkylsilylolefins under Friedel-Crafts conditions give α,β-unsaturated ketones by replacement of the trialkylsilyl group by the acyl group. These reactions proceed under mild conditions, and are highly regioselective. The regioselectivity and the high rates of these reactions are due to the hyperconjugative stabilization of the carbocationic intermediates by the β-silicon substituent (175).



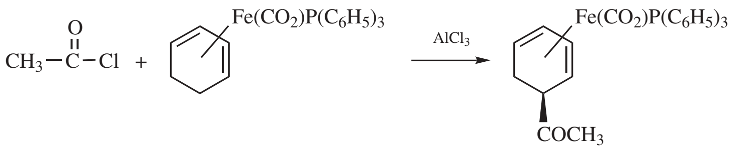
2-Methylcyclobutenyltrimethylsilane undergoes Friedel-Crafts acylation affording the 2-methyl-1-acetylcyclobutene [67223-99-8], which was an intermediate in the synthesis of grandisol [26532-22-9] (176).

Allylsilanes undergo highly regioselective acylation to give β,γ-unsaturated ketones (177). Acylation of γ,γ-dialkylallyltrialkylsilane provides a route to the construction of difficulty accessible quaternary carbon centers.



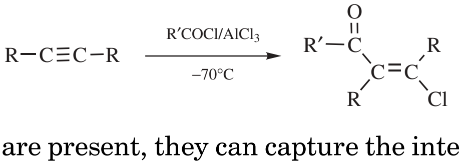
Allylsilanes are more reactive than vinylsilanes in Friedel-Crafts reactions, as shown in the selective acylation of 2,3-disilylalkenes. The allylsilanes, α-silyloxyallyltrialkylsilanes, have been used as enolate equivalents in the preparation of 1,4-diketones (178). The mild reaction conditions required for these reactions tolerate many other functional groups, providing valuable synthetic routes.

Conjugated dienes, upon complexation with metal carbonyl complexes, are activated for Friedel-Crafts acylation reaction at the allylic position. Such reactions are increasingly being used in the stereoselective synthesis of acylated dienes. Friedel-Crafts acetylation of dicarbonyl(η^4-cyclohexadienetriphenylphosphine iron) proceeded under mild conditions in near quantitative yield to give dicarbonyl(η^4-5-*endo*-acetyl) cyclohexa-1,3-dienetriphenylphosphine iron (179).

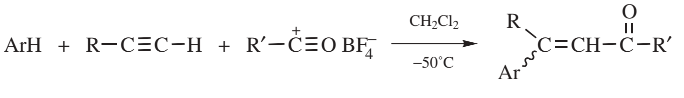


Chiral diene–iron tricarbonyl complexes were acylated using aluminum chloride to give acylated diene–iron complexes with high enantiomeric purity (>96% ee). For example, *trans*-piperylene–iron tricarbonyl reacted with acyl halides under Friedel-Crafts conditions to give 1-acyl-1,3-pentadiene–iron tricarbonyl complex without any racemization. These complexes can be converted to a variety of enantiomerically pure tertiary alcohols (180).

Acylation of acetylenic compounds provides *trans*-β-chlorovinyl ketones (181). Vinyl cations were proposed to be the intermediates in these reactions.



When aromatics are present, they can capture the intermediate vinyl cation to give β-aryl-α,β-unsaturated ketones (182). Thus acylation of alkyl or aryl acetylenes with acylium salts in the presence of aromatics gives α,β-unsaturated ketones with a trisubstituted double bond. The mild reaction conditions employed do not cause direct acylation of aromatics.

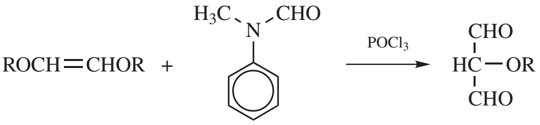


Introduction of a silyl groups at the termini of acetylenes provides a highly selective and mild method for the acylation reactions, the silicon substituent again being replaced by the acyl group. Acylation of bis(trimethylsilyl)ethyne provides terminal alkynyl ketones (183). Macrocyclization of ω-trimethylsilylethynyl alkanoyl chlorides under high dilution conditions provides 11–15 membered cyclic ynones, which are intermediates in the preparation of muscone. The regioselectivity of the reaction is in accordance with the β-carbocation stabilizing influence of the silicon substituent (184).

Even saturated hydrocarbons give ketones with acyl chlorides (20). For example, cyclohexane and acetyl chloride react in the presence of aluminum chloride to give 1-acetyl-2-methylcyclopentane.

Aliphatic Aldehyde Syntheses. Friedel-Crafts-type aliphatic aldehyde syntheses are considerably rarer than those of aromatic aldehydes. However, the hydroformylation reaction of olefins (185) and the related oxo synthesis are effected by strong acid catalysts, eg, tetracarbonylhydrocobalt, $HCo(CO)_4$ (see OXO PROCESS).

The Gattermann-Koch reaction when applied to alkenes or alkanes gives ketones or acids but not aldehydes. However, the Vilsmeier aldehyde synthesis can be applied to aliphatic compounds. For example, 1,2-dialkoxyethylenes react with *N*-methylformanilide and $POCl_3$ to give alkoxymalondialdehydes:



Syntheses of Aliphatic Carboxylic Acids and Derivatives. Alkenes are carbonylated in the presence of acid catalysts at 75–100°C and under pressures of 60–90 MPa (600–900 atm) to give carboxylic acids (186).

$$(CH_3)_2C{=}CH_2 + CO + H_2O \xrightarrow[BF_3{\cdot}2H_2O]{H_2SO_4} (CH_3)_3CCOOH$$

Olefins are carbonylated in concentrated sulfuric acid at moderate temperatures (0–40°C) and low pressures with formic acid, which serves as the source of carbon monoxide (Koch-Haaf reaction) (187). Liquid hydrogen fluoride, preferably in the presence of boron trifluoride, is an equally good catalyst and solvent system (see CARBOXYLIC ACIDS).

Carbocations generated from alkanes using superacids react with carbon monoxide under mild conditions to form carboxylic acid (188). In this process isomeric carboxylic acids are produced as a mixture. However, when the reaction is run with catalytic amounts of bromine (0.3 mmol eq) in HF-SbF_5 solution, regioselective carboxylation is obtained. *n*-Propane was converted almost exclusively to isobutyric acid under these conditions.

Aliphatic Nitration. Alkanes undergo electrophilic nitration with nitronium salts such as $(NO_2)^+$ $(PF_6)^-$ in a protic solvent such as CH_2Cl_2 and sulfolane (189). Adamantane and diamantane have also been nitrated with nitronium tetrafluoroborate in nitromethane solvents (190).

Polymerization. Considerable interest has been focused on olefin polymerizations catalyzed by $AlCl_3$ and BF_3 and a variety of other Lewis-acid halides and protic acids. Three main types are recognized (191): (*1*) conversion of low molecular weight olefins to gasoline-range olefins (192); (*2*) conversion to intermediate molecular weight polymers for use as synthetic lubricant oils; and (*3*) conversion to high molecular weight polymers such as synthetic rubber. Under suitable conditions, the degree of polymerization may be controlled to produce any of the above types. Typical monomers that can readily be converted to high molecular weight polymers are isobutylene, styrene, α-methylstyrene, butadiene, isoprene, and vinyl alkyl ethers.

Even alkanes, when treated with superacids, can undergo oligocondensation. For example, highly branched polyalkanes, of molecular weight up to 700, were obtained by treating gaseous alkanes (C_1–C_4) with liquid superacids at room temperature (81).

Cross-linked macromolecular gels have been prepared by Friedel-Crafts cross-linking of polystyrene with a dihaloaromatic compound, or Friedel-Crafts cross-linking of styrene–chloroalkyl styrene copolymers. These polymers in their sulfonated form have found use as thermal stabilizers, especially for use in drilling fluids (193). Cross-linking polymers with good heat resistance were also prepared by Friedel-Crafts reaction of diacid halides with haloaryl ethers (194).

Friedel-Crafts reaction of naphthalene or tetrahydronaphthalene derivatives with those of styrene or alkylbenzenes has been used in the preparation of high viscous fluids for traction drive (195). Similarly, Friedel-Crafts reaction of tetraline and α-methylstyrene followed by catalytic hydrogenation provided 1-(1-decalyl)-2-cyclohexyl propane, which is used as a highly heat resistant fluid (196).

Hydrocarbon resins (qv) are prepared by copolymerization of vinyltoluene, styrene, and α-methylstyrene in the presence of a Friedel-Crafts catalyst ($AlCl_3$). These resins are compatible with wax and ethylene–vinyl acetate copolymer (197).

Polymer-type antioxidants have been prepared by Friedel-Crafts reaction of *p*-cresol and *p*- and/or *m*-chloromethylstyrene in the presence of boron trifluoride-etherate (198). The oligomeric product resulting from the alkylation of phenyl-α-naphthylamine using C12–15 propylene oligomer in the presence of $AlCl_3$ or activated white clays is used as an antioxidant additive for lubricating oils (199).

4. Catalysts

Friedel-Crafts catalysts are electron acceptors, ie, Lewis acids. The alkylating ability of benzyl chloride was selected to evaluate the relative catalytic activity of a large number of Lewis acid halides. The results of this study suggest four categories of catalyst activity (200) (Table 1).

4.1. Acid Halides (Lewis Acids). All metal halide-type Lewis catalysts, generally known as Friedel-Crafts catalysts, have an electron-deficient central metal atom capable of electron acceptance from the basic reagents. The most frequently used are aluminum chloride and bromide, followed by $BeCl_2$,

Table 1. **Friedel-Crafts Catalyst Activities**

Group	Characteristic	Examples
A	very active, high yields but extensive intra- and intermolecular isomerization	$AlCl_3$, $AlBr_3$, AlI_3, $GaCl_3$, $GaCl_2$, $GaBr_3$, GaI_3, $ZrCl_4$, $HfCl_4$, $HfBr_4$, HfI_4, SbF_5, NbF_5, $NbCl_5$, TaF_5, $TaCl_5$, $TaBr_5$, MoF_6, and $MoCl_5$
B	moderately active, high yields without significant side reactions	$InCl_3$, $InBr_3$, $SbCl_5$, WCl_6, $ReCl_5$, $FeCl_3$, $AlCl_3{-}RNO_2$, $AlBr_3{-}RNO_2$, $GaCl_3{-}RNO_2$, $SbF_5{-}RNO_2$, and $ZnCl_2$
C	weak, low yields without side reactions	BCl_3, BBr_3, BI_3, $SnCl_4$, $TiCl_4$, $TiBr_4$, $ReCl_3$, $FeCl_2$, and $PtCl_4$
D	very weak or inactive	many metal, alkaline-earth, and rare-earth element halides

$CdCl_2$, $ZnCl_2$, BF_3, BCl_3, BBr_3, $GaCl_3$, $GaBr_3$, $TiCl_4$, $ZrCl_4$, $SnCl_4$, $SnBr_4$, $SbCl_5$, $SbCl_3$, $BiCl_3$, $FeCl_3$, and UCl_4.

In addition, boron, aluminum, and gallium tris(trifluoromethanesulfonates) (triflates), $M(OTf)_3$ and related perfluoroalkanesulfonates were found effective for Friedel-Crafts alkylations under mild conditions (200). These Lewis acids behave as pseudo halides. Boron tris(triflate) shows the highest catalytic activity among these catalysts. A systematic study of these catalysts in the alkylation of aromatics such as benzene and toluene has been reported (201).

Easy availability and the low cost of aluminum chloride are partially responsible for its wide use in industry. Although aluminum chloride is frequently thought of as $AlCl_3$, at ordinary temperatures it is, in fact, the dimer Al_2Cl_6, which prevails up to 440°C; between 440 and 880°C there is an equilibrium mixture of monomer and dimer. At higher temperatures, only the monomer exists, although above 1000°C some ionic dissociation takes place. Under the usual Friedel-Crafts reaction conditions, the catalytically active species is always the monomeric Lewis acid $AlCl_3$ (see ALUMINUM COMPOUNDS).

Although Friedel and Crafts in their original work described investigations with anhydrous aluminum chloride, it is very difficult to obtain a Lewis acid-type metal halide in an absolutely anhydrous state and exclude moisture or other impurities during the course of reaction. In view of these facts, it is clear that neither the original inventors, Friedel and Crafts, nor the thousands of subsequent researchers who did most successful work with aluminum chloride and related catalyst systems, worked under truly anhydrous conditions. Impurities such as water, oxygen, hydrogen halides, organic halides, etc, were present in almost all cases. The presence of traces of moisture has been found to accelerate rather than hinder the reactions. In many cases, the presence of these so-called initiators or cocatalysts is indeed essential (202). The beneficial action of traces of moisture has been observed especially in reactions involving the olefinic double bond (alkylation with olefins, polymerization, etc).

The inactivity of pure anhydrous Lewis acid halides in Friedel-Crafts polymerization of olefins was first demonstrated in 1936 (203); it was found that pure, dry aluminum chloride does not react with ethylene. Subsequently it was shown (204) that boron trifluoride alone does not catalyze the polymerization of isobutylene when kept absolutely dry in a vacuum system. However, polymers form upon admission of traces of water. The active catalyst is boron trifluoride hydrate, $BF_3{\cdot}H_2O$, ie, a conjugate protic acid $H^+(BF_3OH)^-$.

Cocatalysts of two types occur: (*1*) proton-donor substances, such as hydroxy compounds and proton acids, and (*2*) cation-forming substances (other than proton), including alkyl and acyl halides which form carbocations and other donor substances leading to oxonium, sulfonium, halonium, etc, complexes.

4.2. Metal Alkyls and Alkoxides.

Metal alkyls (eg, aluminum boron, zinc alkyls) are fairly active catalysts. Hyperconjugation with the electron-deficient metal atom, however, tends to decrease the electron deficiency. The effect is even stronger in alkoxides which are, therefore, fairly weak Lewis acids. The present discussion does not encompass catalyst systems of the Ziegler-Natta type (such as $AlR_3 + TiCl_4$), although certain similarities with Friedel-Crafts systems are apparent.

The most important application of metal alkoxides in reactions of the Friedel-Crafts type is that of aluminum phenoxide as a catalyst in phenol alkylation (205). Phenol is sufficiently acidic to react with aluminum with the formation of $(C_6H_5O)_3Al$. Aluminum phenoxide, when dissolved in phenol, greatly increases the acidic strength. It is believed that, similar to alkoxoacids (206) an aluminum phenoxoacid is formed, which is a strong conjugate acid of the type $HAl(OC_6H_5)_4$. This acid is then the catalytically active species (see ALKOXIDES, METAL).

4.3. Protic Acids (Brønsted Acids).

Sulfuric acid is among the most used Brønsted acids for the Friedel-Crafts reactions, especially in hydrocarbon conversions, and in alkylation for the preparation of high octane gasoline. Anhydrous HF has replaced in part sulfuric acid, because of its convenience, although the toxic hazardous nature of HF is causing environmental concerns in its industrial use. Trifluoromethanesulfonic acid [1493-13-6] (and related superacids) are also gaining significance. Triflic acid does not react with aromatics (whereas sulfuric acid causes sulfonation) and thus offers substantial advantages with aromatic systems.

4.4. Acidic Oxides and Sulfides (Acidic Chalcogenides).

Chalcogenide catalysts include a great variety of solid oxides and sulfides; the most widely used are alumina or silica (either natural or synthetic), in which other oxides such as chromia, magnesia, molybdena, thoria, tungsten oxide, and zirconia may also be present, as well as certain sulfides such as sulfides of molybdenum. The composition and structure of different types of bauxites, floridin, Georgia clay, and other natural aluminosilicates are still not well known. Some synthetic catalysts, other than silica–alumina compositions, representative of the acidic chalcogenides are BeO, Cr_2O_3, P_2O_5, TiO_2, and $Al_2(SO_4)_3$ which may be regarded as Al_2O_3, $3SO_3$, $Al_2O_3 \cdot xCr_2O_3$, $Al_2O_3 \cdot Fe_2O_3$, $Al_2O_3 \cdot MnO$, $Al_2O_3 \cdot CoO$, $Al_2O_3 \cdot Mo_2O_3$, $Al_2O_3 \cdot V_2O_3$, $Cr_2O_3 \cdot Fe_2O_3$, MoS_2, and MoS_3. In contrast to sulfuric acid which may be regarded as a fully hydrated chalcogenide, the members of this group are seldom very highly hydrated under conditions of use.

Silica–alumina has been studied most extensively. Dehydrated silica–alumina is inactive as isomerization catalyst but addition of water increases activity until a maximum is reached; additional water then decreases activity. The effect of water suggests that Brønsted acidity is responsible for catalyst activity (207). Silica–alumina is quantitatively at least as acidic as 90% sulfuric acid (208).

4.5. Acidic Cation-Exchange Resins. Brønsted acid catalytic activity is responsible for the successful use of acidic cation-exchange resins, which are also solid acids. Cation-exchange catalysts are used in esterification, acetal synthesis, ester alcoholysis, acetal alcoholysis, alcohol dehydration, ester hydrolysis, and sucrose inversion. The solid acid type permits simplified procedures when high boiling and viscous compounds are involved because the catalyst can be separated from the products by simple filtration. Unsaturated acids and alcohols that can polymerize in the presence of proton acids can thus be esterified directly and without polymerization.

Sulfonated styrene–divinylbenzene cross-linked polymers have been applied in many of the previously mentioned reactions and also in the acylation of thiophene with acetic anhydride and acetyl chloride (209). Resins of this type (Dowex 50, Amberlite IR-112, and Permutit Q) are particularly effective catalysts in the alkylation of phenols with olefins (such as propylene, isobutylene, diisobutylene), alkyl halides, and alcohols (210) (see ION EXCHANGE).

4.6. Superacids. *Brønsted Superacids.* In the 1960s a class of acids hundreds of millions times stronger than mineral acids was discovered; acids stronger than 100% sulfuric acid are called superacids (211). The determination of acidity by pH measurement does not hold for very concentrated acid solution. Hammett's logarithmic acidity function is generally used (212).

$$H_o = pK_{BH}^{+} - \log\frac{BH^+}{B}$$

where pK_{BH}^{+} is the dissociation constant of the conjugate acid and $\frac{BH^+}{B}$ is the ionization ratio. Typical H_o values are −12.6 for 100% H_2SO_4, and −11.0 for anhydrous HF. Although more recent H_o measurements on completely anhydrous HF have shown acidities comparable to that of FSO_3H (−15.1) (213).

Fluorosulfuric acid [7789-21-1] (HSO_3F) is one of the strongest Brønsted acids known with $H_o = -15.1$. This acidity is somewhat lower than that of H_2SO_4–SO_3, ie, $H_2S_2O_7$. However, because of its stability, ease of purification, its wide liquid range (mp = −89°C, bp = 162°C) and relatively low viscosity (1.56 mPa·s(=cP) at 28°C), it is more convenient to use.

Perfluoroalkanesulfonic acids also show high acidity. The parent trifluoromethanesulfonic acid (triflic acid), CF_3SO_3H, is commercially prepared by electrochemical fluorination of methanesulfonic acid (214). It has an H_o value of −14.1 (215, 216). The higher homologues show slightly decreasing acidities.

4.7. Super Lewis Acids. Acid systems stronger than anhydrous $AlCl_3$ are classified as super Lewis acids (211). By this definition, Lewis acids such as SbF_5, NbF_5, AsF_5, and TaF_5 are so categorized.

4.8. Brønsted-Lewis Superacids. Conjugate Friedel-Crafts acids prepared from protic and Lewis acids, such as HCl–$AlCl_3$ and HCl–$GaCl_3$ are, indeed, superacids with an estimated H_o value of −15 to −16 and are effective catalysts in hydrocarbon transformation (217).

In the early 1960s acid systems were prepared comprising a pentafluoride of group V elements, particularly SbF_5 and a strong Brønsted acid such as HF,

FSO_3H, CF_3SO_3H, etc (218). Magic Acid [33843-68-4] (HSO_3F-SbF_5) is one of the strongest members of the system; fluoroantimonic acid [16950-06-4], $HF-SbF_5$, even surpasses Magic Acid in its acidity. The acidity of HF or HSO_3F is increased sharply by adding SbF_5 (219,220). These very highly acidic systems are being utilized in transformations such as isomerization of straight-chain alkanes (221), Alkane–alkene alkylations (222), and the like (223). $CF_3SO_3H-SbF_5$ and $CF_3SO_3H-B(OTf)_3$ have been shown to be highly effective catalysts for Friedel-Crafts alkylation and isomerization reactions (224).

4.9. Solid Superacids. Most large-scale petrochemical and chemical industrial processes are preferably done, whenever possible, over solid catalysts. Solid acid systems have been developed with considerably higher acidity than those of acidic oxides. Graphite-intercalated $AlCl_3$ is an effective solid Friedel-Crafts catalyst but loses catalytic activity because of partial hydrolysis and leaching of the Lewis acid halide from the graphite. Aluminum chloride can also be complexed to sulfonate polystyrene resins but again the stability of the catalyst is limited.

More stable catalysts are obtained by using fluorinated graphite or fluorinated alumina as backbones, and Lewis acid halides, such as SbF_5, TaF_5, and NbF_5, which have a relatively low vapor pressure. These Lewis acids are attached to the fluorinated solid supports through fluorine bridging. They show high reactivity in Friedel-Crafts type reactions including the isomerization of straight-chain alkanes such as *n*-hexane.

Another type of solid superacid is based on perfluorinated resin sulfonic acid such as the acid form of Du Pont's Nafion resin, a copolymer of a perfluorinated epoxide and vinylsulfonic acid or solid, high molecular weight perfluoroalkanesulfonic acids such as perfluorodecanesulfonic acid, $CF_3(CF_2)_9SO_3H$. Such solid catalysts have been found efficient in many alkylations of aromatic hydrocarbons (225) and other Friedel-Crafts reactions (226).

4.10. Superacidic Zeolites. The well-defined crystal structures of both natural and synthetic zeolites permit selective hydrocarbon transformations. The selectivity of the zeolites can be improved by deactivations of external acid sites with amines, replacement of the cationic sites by transition metal ions by ion-exchange, or by modification of the silica–alumina ratio. Some zeolites such as H-ZSM-5 and the like display superacidic character at high temperatures (see MOLECULAR SIEVES). The have found wide utility in electrophilic aromatic alkylations, transalkylations, disproportionation, hydrocarbon synthesis, and more importantly, methanol conversion to hydrocarbons, including fuel gas and gasoline (227). H-ZSM-5 was also used as an efficient catalyst for the thermal degradation of polypropylene into gasoline range hydrocarbons (228). Various pillared clays obtained by reaction of metal trihalides with the hydroxyl groups on clays act as selective catalysts, especially in transalkylations (229).

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