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# Bond Activation by Germanium Complexes

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## *ABSTRACT*

There have been 118 elements discovered which can combine to form thousands of different molecules with many different properties. Metalloids are very important elements, because they contain properties of both metals and nonmetals. Germanium is a metalloid that has historically found many uses, including the increasingly important use in organometallic complexes used for bond activation. In order to evaluate Germanium's ability to activate bonds, we looked at triphenyl germanium hydride. This molecule contained many of the important properties, including sterically bulky ligands, which make it a successful organometallic compound. This compound was found to successfully activate the increasingly important carbon to fluorine bonds found in benzoyl fluoride, as well as a variety of fluorinated aromatic compounds. These reactions followed different mechanisms, though. With benzoyl fluoride, triphenyl germanium hydride was paired with a weakly-coordinating anion (WCA) in order for a Lewis acid mechanism to take place. With the aromatic compounds, 1,1'-Azobiscyclohexanecarbonitrile (AHCN) was used for a free-radical polymerized reaction to occur. By understanding how these reactions successfully took place, we can evaluate other bond types and reactions that can be activated by the tri-phenyl germanium complex. Some of the explored bonds in this paper include: amide bond activation through the Lewis acid mechanism, and carbon to hydrogen bond activation via the radical pathway or through the altering of bond orbitals and polarity.

## *INTRODUCTION*

There have been 118 elements discovered, and they can combine to form thousands of different compounds and molecules with many different properties. These compounds that are formed make up all of the things around us, living and non-living, including ourselves. Humans are made up almost completely of just four elements: carbon, nitrogen, oxygen, and hydrogen. While it is very important to understand these four elements, how they react together, and their properties, it is increasingly important to understand the other 114 elements as well. Understanding the other elements found in the periodic table allows us to find ways to manipulate and react with those four elements and the bonds which they form. Some of these bonds are extremely difficult to break or form naturally, so knowing the properties of other elements and their capabilities are necessary to find new ways to manipulate the bonds.

### *METALLOIDS*

The periodic table is split into three main groups; metals, metalloids, and nonmetals. Metals are elements that are good conductors of heat and electricity, while nonmetals are poor conductors of heat and electricity. Metalloids are elements that have properties of both metals and nonmetals, which makes them semiconductors. A metalloids activity can depend on the different molecules and elements that it is reacted with or the environmental conditions. For example, when a metalloid is reacted with a metal it will act as a nonmetal. When a metalloid is reacted with a nonmetal it will act as a metal. Other physical or chemical properties of the environment of a metalloid can affect its activity, like pH, temperature, etc. The most common metalloids that are studied today are Arsenic (As), Antimony (Sb), Tellurium (Te), Boron (B), Germanium (Ge), Silicon (Si), and sometimes Astatine (At), and Selenium (Se).[1] In the past, a lot of metalloids were used for medicinal purposes but are used for a variety of different purposes today.[1] Now, they are mostly used as components of semiconductor devices, ceramics,

solar batteries, components of polymers, construction material, agriculture, and still sometimes used in medicine.[1]

*GERMANIUM*

Germanium, a metalloid found in group 14 of the periodic table, was discovered in 1886 by Clemens Winkler.[2] Its first main use was as the semiconductor in Schottky diodes that were used for radar reception in World War II.[2] After the addition of a third connection, the first electronic amplifier device was invented, the transistor.[2] Being used in transistors was one of the most common applications of the Germanium element for many years. It was believed that Germanium was a poorly conducting metal until the late 1930's. [2] Now, different forms of Germanium have many different uses. Germanium oxide, $GeO_2$, has properties that reveal a high index of refraction and dispersion making the molecule important for use in wide-angle camera lenses and for objective lenses in microscopes.[3] Germanium is also a good alloying agent, meaning that when it is mixed with another substance it has some superior properties.[3] Germanium can be used as a catalyst for reactions like in diamond synthesis.[4] Certain Germanium compounds have been found to have a low toxicity in mammals and are thought to be effective against some bacteria which has led to an increased study in pharmaceutical use of germanium.[3] For example, Germanium sesquioxide, $Ge_2O_3$ (figure 1), has been studied as a supplement used for different cancer symptoms.[5] Due to the amount of oxygens in the molecule, germanium sesquioxide is a very efficient donor of electrons. This makes it possible for the molecule to merge with free radicals and also possible to eliminate radicals from the body of the organism.[5] The molecule also helps the body by enhancing its natural defense against disease and aging.[5] Other important uses of germanium include propagermanium, organic germanium, or betacarboxyethlgermanium sesquioxide used as complementary medicines that are helpful in boosting the immune system for cancer patients.[5] These germanium compounds have also been

used to assist in the treatment of AIDs, some heart diseases, and in arthritis.[5] As well as for the purpose of boosting the immune system, germanium nanoparticles have been discovered to be useful as a potential spleen imaging agent.[5] Only inorganic germanium compounds have been found to contain the radio sensitizing effect in cells. [5]

*ORGANOMETALLIC COMPLEXES*

The use of metalloids as metals in organometallic complexes has become increasingly important for bond activation. The activation of different bonds in biologically active compounds can be very important for the synthesis or decomposition of important molecules. Historically, organometallic compounds are found to have a center containing a metal or metal-like atom which interacts with the substrate.[6] Bonded to the metal center are the ligands, which can affect the reactivity of the complex by electronically or sterically influencing interactions, but not coming into direct contact with the substrate.[6] In metal complexes, electronic unsaturations can have a big effect on the reactivity of the organometallic complex toward other molecules.[7] Electronic unsaturations in organometallic complexes are due to the metal atom not containing a full set of 18 electrons. The more electronic unsaturations found in an organometallic complex, the more catalytic properties the complex has. One way to induce electronic unsaturations is to use sterically bulky ligands which cover a majority of the space surrounding the metal atom.[7] With a large amount of the space of the metal atom blocked, a full ligand is prevented from binding to the atom but there is still potentially space to bind or activate other small molecules.

*BOND ACTIVATION*

The synthetic mechanism of bond activation is found to be very important in carbon to fluorine bonds. Carbon to fluorine bonds are very important due to the highly electronegative

properties of fluorine, creating a very strong covalent bond between the two atoms. [8] As a result of the strong electronic pull from fluorine, carbon to fluorine bonds are very polar and have low polarizability. These properties make the bonds very strong and generally unreactive. These properties make fluorinated compounds long-lived and potentially toxic, contributing to the production of greenhouse gases and global warming.[8] The use of organometallic compounds to develop synthetic methods to activate these bonds are therefore very important due to the environmental concerns associated with the strong carbon to fluorine bond. It has also been shown that carbon to fluorine bonds can be important in pharmaceuticals because fluorine can enhance the binding effectiveness and selectivity in pharmaceuticals.[9] Due to the high electronegativity of fluorine, fluorine substituents will be directed toward electropositive regions on receptor sites.[9] This organization can enhance the molecules lipophilicity and the ability to dissolve in non-polar solvents. For this to happen, the fluorine atom will undergo multipolar interactions with atoms in many different biologically important bonds. Some include the hydrogen in a nitrogen to hydrogen peptide bond, the carbon in a carbonyl peptide bond, or the hydrogen in carbon to hydrogen peptide bonds as well as in amide side chains of certain amino acids.[9] The increased lipophilicity can strengthen protein-ligand interactions and can affect the absorption, distribution, metabolism, excretion, and toxicity of pharmaceuticals, making carbon to fluorine bond activation a very important topic of research.

## *METHODS AND RESULTS*

### *HYDRODEFLUORINATION*

One of the experiments that we worked on to evaluate the bond activation of carbon to fluorine bonds was the hydrodefluorination of benzoyl fluoride by a germanium hydride (reaction 1). For hydrodefluorination to successfully occur, it is required to have a very strong

Lewis acid which also has a strong affinity for fluorine.[8] The driving force of these types of reactions is the covalent formation of a more stable bond to the fluorine atom.[8] The germanium hydride used to complete these reactions was triphenyl germanium hydride. Triphenyl germanium hydride is a good organometallic compound for hydrodefluorination reactions because the three phenyl groups attached to the germanium are sterically bulky, creating unsaturation's which make the germanium very reactive toward small molecules. These unsaturation's which make the Germanium complex more reactive are also what make the complex work as a Lewis acid.

Another important part to this reaction in order to successfully defluorinate benzoyl fluoride is the use of a weakly coordinating anion. The weakly coordinating anion is needed for triphenyl germanium hydride to successfully donate its hydrogen and become triphenyl germanium cation and remain stabilized by the weakly coordinating anion. In order for the triphenyl germanium cation to remain stable but also still have potential for reacting with the fluorine in benzoyl fluoride, the weakly coordinating anion had to have properties allowing it to stabilize the germanium cation without having any other significant interactions. In these reactions we tested the optimization of the reaction by testing different weakly coordinating anions and finding the percent yield for each reaction. When testing the different anions, we used benzene as the solvent and kept the reaction at room temperature. It was found that in these conditions $B(C_6F_5)_4$ was the only weakly coordinating anion that allowed the reaction to successfully occur (Table 1).[10] With $BF_4$ as the weakly coordinating anion there was found to be a 0% yield of the desired products (Table 1).[10] When $SnCl_5$ was used as the weakly coordinating anion, there was no reaction completed (Table 1).[10]

Other parts to the reaction that were tested in the optimization reactions were the solvents used and the temperature that the reactions were reacted in. Since $B(C_6F_5)_4$ was found to be the most successful weakly coordinating anion, it was used in the reactions to test the optimal temperature and solvent. The different solvents that were tested were benzene, hexane, toluene, acetonitrile, and in neat (solvent-free) conditions. For hydrodefluorination to occur it is also important to have a weakly coordinating solvent, meaning that its charge is delocalized over the entire surface and not just on one atom. This avoids any interactions with the germanium cation. In the reactions, it was determined that the best conditions for the reaction to occur was in neat, solvent-free, conditions because there was no solvent to interact with the cation (Table 1).[10] After neat conditions, the best solvent was found to be benzene (Table 1).[10] When testing which temperature the reaction occurred best at, the solvent used was benzene and the weakly coordinating anion used was $B(C_6F_5)_4$. The reaction was tested at room temperature and in reflux (heat). It was found that the reaction had a much higher percent yield, 67.72%, at room temperature compared to the reaction done in reflux which had 26.44% yield (Table 1). [10]

Another project that we worked on in order to evaluate the reactivity of triphenyl germanium hydride for bond activation was with fluorinated ring compounds. The driving force in these reactions was also the formation of strong germanium to fluoride bonds, replacing the fluorine on the ring with hydrogens. Instead of using a weakly coordinating ion to stabilize the triphenyl germanium cation, in these reactions we used 1,1'-Azobiscyclohexanecarbonitrile (AHCN) for a free-radical polymerized reaction. Although we know that these reactions do successfully defluorinate the ring due to the presence of triphenyl germanium fluoride in the product, it is not completely clear what the other products were. We used pentafluoronitrobenzene and believe to have a product of nitrobenzene (reaction 2).

Pentafluoroaniline was reacted to obtain an expected product of 2,3,5,6-tetrafluoroaniline (reaction 3). Next, hexafluorobenzene was reacted and thought to produce benzene as a product (reaction 4). Octafluorotoluene was expected to react to form trifluorotoluene (reaction 5). Finally, Pentaluorotoluene was reacted and expected to have a product of toluene (reaction 6). initiator

## *DISCUSSION*

After completing the reactions discussed, we can use the information gathered about bond activation by germanium hydrides and use it to develop future uses. One of the first future applications that we can evaluate is the activation of different bond types. To determine different types of bonds that these same methods of activation could work on, we first look at the standard bond energies. The standard bond energy is the energy required to break a covalent bond. The standard bond energy of carbon to fluorine bonds is 116 kcal/mole.[11] To determine which type of bonds could potentially be activated by the same mechanism as the carbon to fluorine bonds we should look at bonds that have a standard bond energy similar to that of the carbon to fluorine bonds. Some examples are: oxygen to hydrogen bonds which have a standard bond energy of 111 kcal/mole, oxygen to carbonyl bonds which have a standard bond energy of 110 kcal/mole, carbon to hydrogen bonds which have a standard bond energy of 99 kcal/mole, and nitrogen to carbonyl bonds which have a standard bond energy of 89 kcal/mole.[11] It is important to remember that single bonds are weaker than double bonds, which are weaker than triple bonds. This is because in single bonds you are only required to have the energy to break a single sigma bond. In double bonds you are required to have the energy to break the single sigma bond along with a single pi bond. In triple bonds you are required to have the energy to break the sigma bond along with two pi bonds. The extra pi bonds in double and triple bonds makes the bond

between two atoms stronger and pull them closer together, making it harder to break. The extra energy needed to break the pi bonds makes some double or triple bonds have a standard bond energy similar to that of the single bond of carbon to fluorine bonds. For example, a nitrogen double bonded to a nitrogen has a standard bond energy of 109 kcal/mole and an oxygen double bonded to an oxygen has a standard bond energy of 119 kcal/mole.[11]

The difference between the double bonded oxygens and the double bonded nitrogen example compared to the carbon to fluorine bonds is the way that the atoms share electrons in the bond. In carbon to fluorine bonds, carbon and fluorine have different electronegativities, meaning they have varying strengths in the ability to attract electrons. Fluorine is much more electronegative than carbon allowing fluorine and carbon to have an unequal sharing of electrons in the bond which they share, making it a polar bond. This property is also found in the oxygen to hydrogen bonds, oxygen to carbonyl bonds, and the nitrogen to carbonyl bonds, but not in the carbon to hydrogen bonds. In the carbon to hydrogen bonds the carbon and hydrogen have similar electronegativity values, so one does not have an extreme pull of electrons over the other. That makes the carbon to hydrogen bonds non-polar. In the double bonded oxygens and double bonded nitrogen, they also have an equal share of electrons in the bonds since they are the same atoms, and therefore have the same electronegativity, so they are also non-polar bonds.

The nitrogen to carbonyl bonds discussed are called amide bonds and are very important in biomolecules like peptides, proteins, DNA, and RNA. There has already been research examining the activation of amide bonds via metal complexes. We can use the information gathered to evaluate if the amide bond could be activated by the triphenyl germanium hydride. The widely reported approach for amide bond activation is through distortion of the bond so that the amide can no longer form its resonance structure. [12] By distorting the amide bond it also loses

its double bond character, allowing it to become more vulnerable to a nucleophilic or electrophilic attack.[12] There have been many different metal complexes that have been tested for activating amide bonds, and most of the studied approaches are based on the activation of the amide carbonyl by a Lewis acid mechanism.[12] When examining the mechanisms of bond activation for amide bonds in peptides, the side chains of different amino acids and the environment of the reaction can play a part in the way that the metal complex reacts. For example, an experiment looking at the $Pd(H_2O)_4$ complex's ability to hydrolyze an amide bond in a decapeptide in acidic conditions takes place at a different amino acid residue than when in neutral conditions.[12] When in acidic conditions, the cleavage of the peptide bond occurred at a Glycine residue next to a Methionine on the N-terminal end, creating two peptide fragments. [12] In neutral conditions, it was observed that the rate of cleavage was much slower compared to the lower pH conditions in the acidic experimental conditions.[12] It was also discovered that in the neutral conditions there was no cleavage seen between a Glycine and Methionine residue like in the acidic conditions. Although there was no cleavage observed between the Glycine and Methionine in neutral conditions, cleavage was observed between a Sarcosine and Methionine residue as well as in between a Proline and Methionine residue.[12] This is due to the equilibrium of the Glycine-Methionine in neutral conditions being shifted to a more inactive form which allows the Glycine residue to form a strong coordinate bond with the Pd in the metal complex.[12] In the reactions using triphenyl germanium hydride for hydrodefluorination of benzoyl fluoride, the metal complex was able to react as a Lewis acid because the hydrogen was given up and then the presence of a weakly coordinating anion was able to stabilize the cation allowing it to act as a Lewis acid. With this same mechanism or something similar it may be possible to activate

certain amide bonds in peptides, depending on the conditions of the reaction and the side chains that are present in the molecule.

Carbon to hydrogen bonds are the main constituents of alkanes which are a big part of natural gas and petroleum. Carbon to hydrogen bond activation is something that is very difficult because reactions of alkanes occur at high temperatures, are not readily controlled, and usually produce economically unattractive products.[13] Using metal centers to activate small inert molecules has found to be a successful mechanism due to the changes in the energy of the bonds orbitals and polarity.[13] This same mechanism should make it possible to activate carbon to hydrogen bonds which are small inert bonds, the only problem is that carbon to hydrogen bonds lack lone electron pairs and pi orbitals which could interact with the metal centers. In pre-1980 research it was found that carbon to hydrogen bonds could be activated through metal centers if they were assisted by the participation of pi orbitals in aromatic carbon to hydrogen bonds or if intramolecular interactions were involved.[13] It has also been thought that many times carbon to hydrogen bond activation might have taken place, but the products yield an organometallic product which is not thermodynamically stable and therefore is undetectable in the products.[13] There are many difficult aspects to bond activation of carbon to hydrogen bonds, and thermodynamics is one of the most complicated. Selectivity of where the molecule is reacted is also very challenging. If the desired product has a functional group that reacts more readily with the metal complex than the alkane in the starting material then activation can be very difficult.[13] Another issue with the selectivity in carbon to hydrogen bond activation is that when the reaction is proceeding via a radical pathway, the terminal positions are the least reactive. Therefore, the reactivity of different carbon to hydrogen bonds throughout the alkane can be an issue.[13] It has been observed, though, that metal centers activate terminal carbon to hydrogen bonds in contrast

to the radical pathway.[13] For example, in a reaction using a Rhodium metal complex there was found to be 100% primary alkyl groups in the product.[13] In another experiment using an Iridium metal complex there was found to be around 70-80% primary alkyl groups, depending on the length of the alkyl chain.[13]

## *Conclusion*

By evaluating the properties of successful organometallic complexes and the mechanisms that they follow, we are able to apply our knowledge to find future possible methods of bond activation. Now that we know that triphenyl germanium hydride has enough unsaturations provided by the three sterically bulky phenyl groups attached, we can use this complex as well as similar complexes to activate important bonds. After completing the hydrodefluorination experiments, we better understand the properties of the reactions which allow the strong carbon to fluorine bonds to be activated. We can now evaluate other bond types, similar to the carbon to fluorine bonds, and hypothesize the mechanisms which they could potentially be activated by germanium complexes. When evaluating the amide bonds and the possibility to activate them, we may expect to use a similar Lewis acid mechanism as the reaction with benzoyl fluoride. When evaluating carbon to hydrogen bonds, we may expect to use a mechanism similar to the free-radical polymerized reactions with the aromatic fluorinated compounds. There are many other possibly mechanisms, organometallic complexes, and bonds which could be activated. By further understanding the complexes, mechanisms, and bonds mentioned in this paper, we can more easily and accurately predict ways to accomplish these future reactions.

## *Figures*

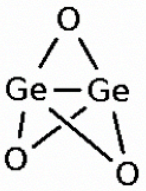
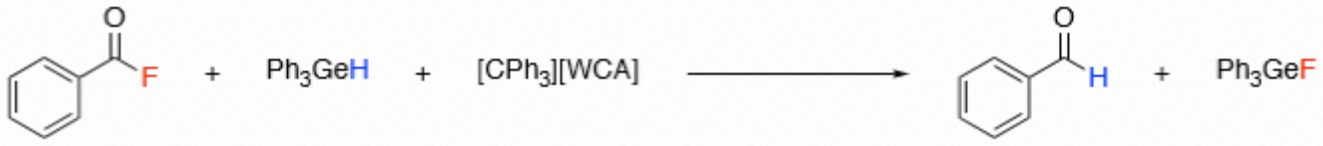


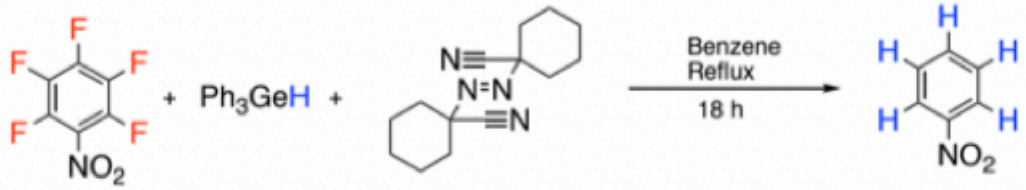

Figure 1. Molecular structure of germanium sesquioxide

| 03_016_# | Solvent | WCA | Temperature | Time | % Yield |
|---|---|---|---|---|---|
| 1 | Benzene | $B(C_6F_5)_4$ | RT | 18 h | 67.72 |
| 2 | Hexane | $B(C_6F_5)_4$ | RT | 18 h | 30.49 |
| 3 | Toluene | $B(C_6F_5)_4$ | RT | 18 h | 49.76 |
| 4 | Acetonitrile | $B(C_6F_5)_4$ | RT | 18 h | 27.81 |
| 5 | Neat | $B(C_6F_5)_4$ | RT | 18 h | 87.13 |
| 6 | Benzene | $SnCl_5$ | RT | 18 h | N.R |
| 7 | Benzene | $BF_4$ | RT | 18 h | 0 |
| 8 | Benzene | $B(C_6F_5)_4$ | Reflux | 18 h | 26.44 |

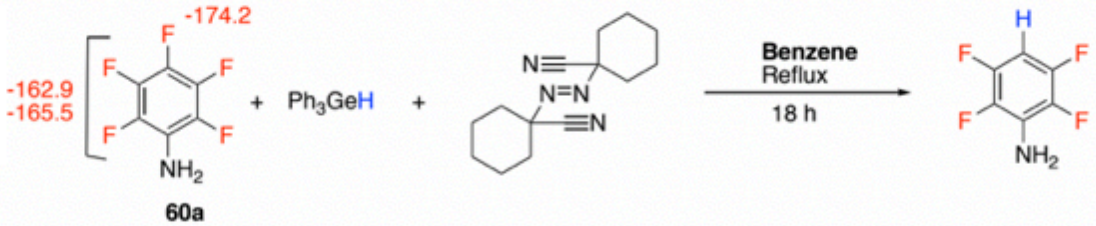
Table 1. A summary of the results from the optimization reactions from the HDF by triphenyl germanium cation



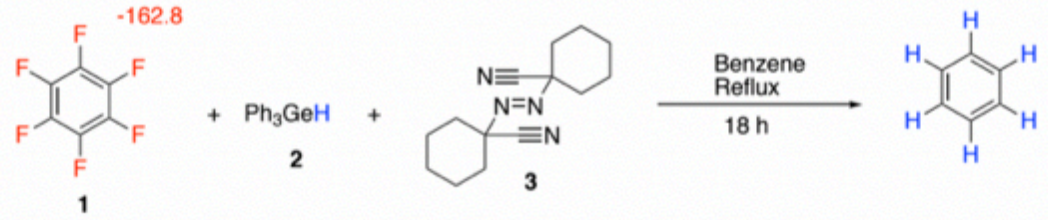

Reaction 1. The general reaction for the HDF by triphenyl germanium cation reactions. The solvent, WCA, and temperature were adjusted to determine the best conditions for highest percent yield.



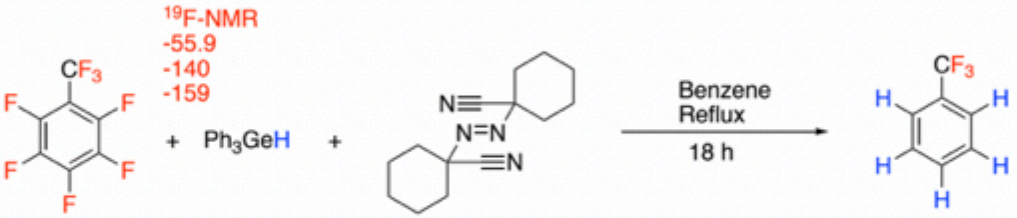

Reaction 2. Pentafluoronitrobenzene expected to react with triphenyl germanium hydride to produce nitrobenzene



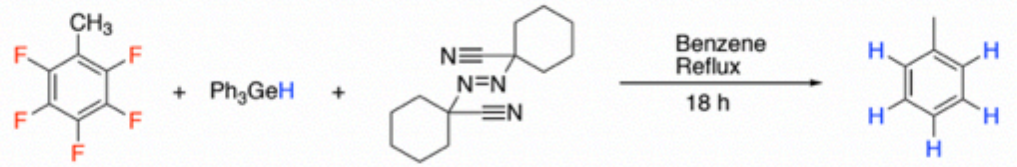

Reaction 3. Pentafluoroaniline expected to react with triphenyl germanium hydride to produce 2,3,5,6-tetrafluoroaniline




REACTION 4. HEXAFLUOROBENZENE EXPECTED TO REACT WITH TRIPHENYL GERMANIUM HYDRIDE TO PRODUCE BENZENE




REACTION 5. OCTAFLUOROTOLUENE EXPECTED TO REACT WITH TRIPHENYL GERMANIUM HYDRIDE TO PRODUCE TRIFLUOROTOLUENE




REACTION 6. PENTAFLUOROTOLUENE EXPECTED TO REACT WITH TRIPHENYL GERMANIUM HYDRIDE TO PRODUCE TOLUENE

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