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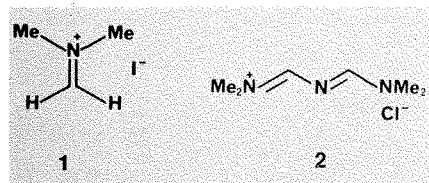
# Some Useful Synthetic Applications of Gold's Reagent

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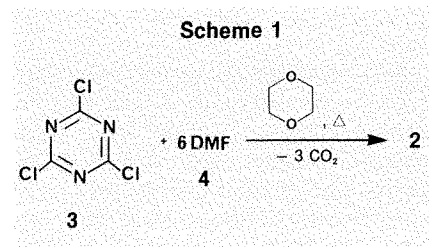
## Introduction

While looking for some appropriate research projects, I had been impressed by and interested in the work of Danishefsky<sup>1</sup> and others<sup>2</sup> regarding the use of "Eschenmoser's salt" (1). During the course of a literature search on an industrial project, we came across an article by Gold,<sup>3</sup> which described the preparation of a rather interesting vinylogous iminium salt (2). The name assigned to this compound was [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride. This terminology seemed a little cumbersome for routine discussions so we adopted the name "Gold's Reagent" for compound 2. Although the reagent had been prepared<sup>3</sup> in 1960, very little research<sup>4</sup> had been performed on this substance in the intervening years. We therefore decided to begin an exhaustive study to delineate and define what, if any, useful synthetic chemistry could be developed from Gold's Reagent.



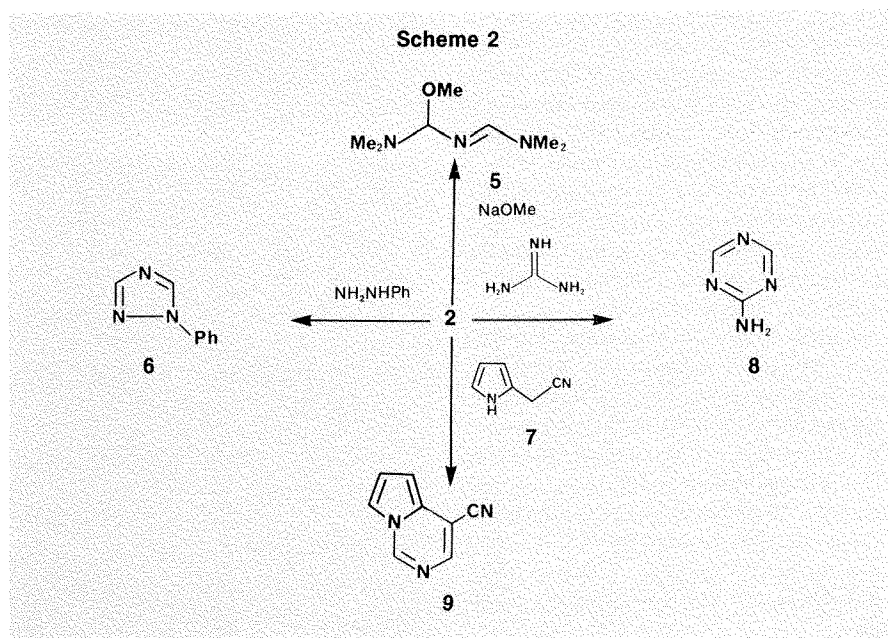
## Preparation and properties

Gold's Reagent is easily prepared<sup>5</sup> in nearly quantitative yield by treating one equivalent of cyanuric chloride (3) with six equivalents of *N,N*-dimethylformamide (4) in an inert solvent such as dioxane (Scheme 1). After heating the mixture for approximately 30-40 minutes, an exothermic reaction ensues<sup>6</sup> evolving three equivalents of carbon dioxide over a 1- to 2-hour period. On cooling the dark solution to room temperature, a tan to dark-brown solid (2) rapidly forms. This material is isolated by either 1) rapid filtration and washing with acetone or 2) removal of solvents *in vacuo*, and then drying under vacuum. This tan to brown solid is very hygroscopic but can be stored indefinitely in a dry environment. Gold's Reagent is soluble in water and chloroform but is not soluble in any of the normal, nonpolar organic solvents. Based on its NMR spectrum,<sup>5</sup> it is assumed to have the W-configuration.



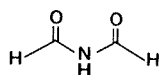
## Initial work by Gold and others

In his initial report,<sup>3</sup> Gold demonstrated that this vinylogous iminium system would react with alkoxide ion, guanidine and phenylhydrazine (Scheme 2). In 1974 Jutz<sup>4</sup> and coworkers studied the reaction of 2 with 2-cyanomethylpyrrole (7). In all cases which had been studied up to this point, it appeared that the CH=N-CH unit of Gold's Reagent had been incorporated into the reaction product with the loss of two equivalents of dimethylamine.



## Recent work

Gold's Reagent can be viewed formally as a 3-azavinamidinium salt<sup>7</sup> and can be represented by the contributing resonance structures shown in Scheme 3. Interestingly, Gold's Reagent, as well as other vinamidinium compounds can also be viewed as a masked 1,3-dicarbonyl system. The vinamidinium system possesses some advantages over analogous 1,3-dicarbonyl compounds in reactions with nucleophiles, since deprotonation of N-H cannot occur.

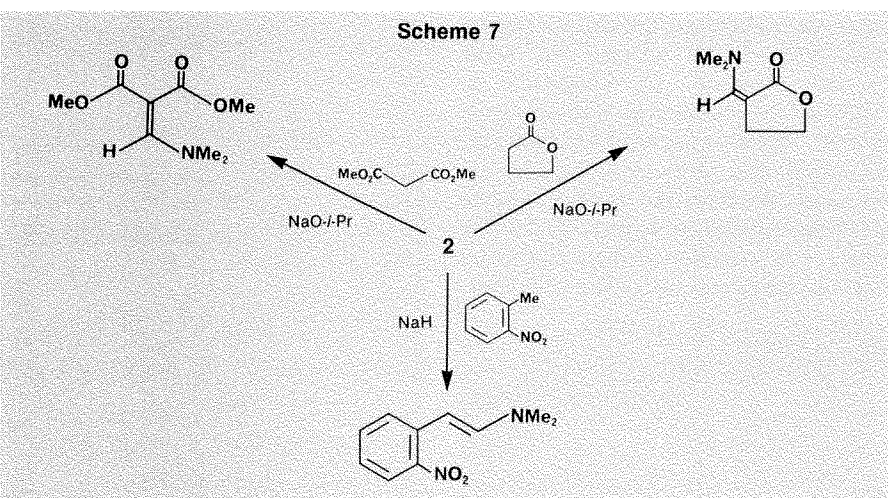
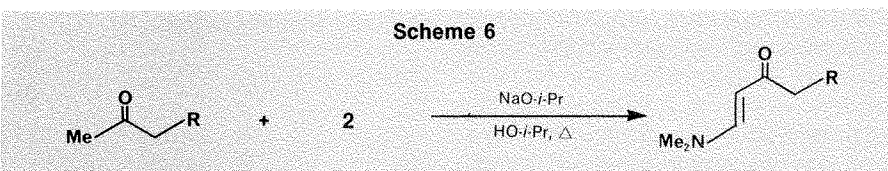
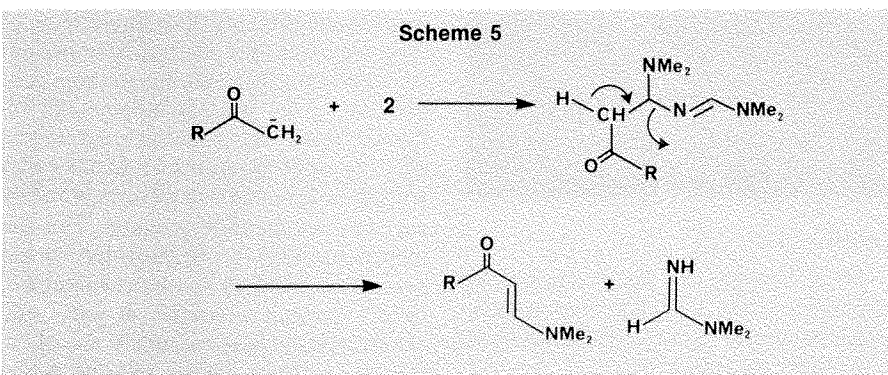
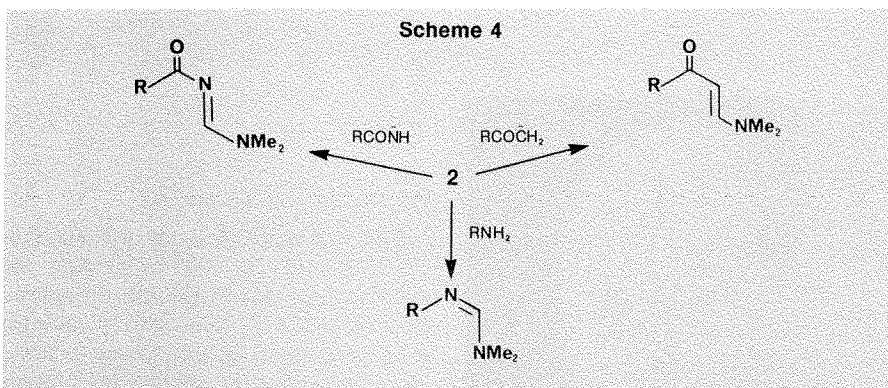
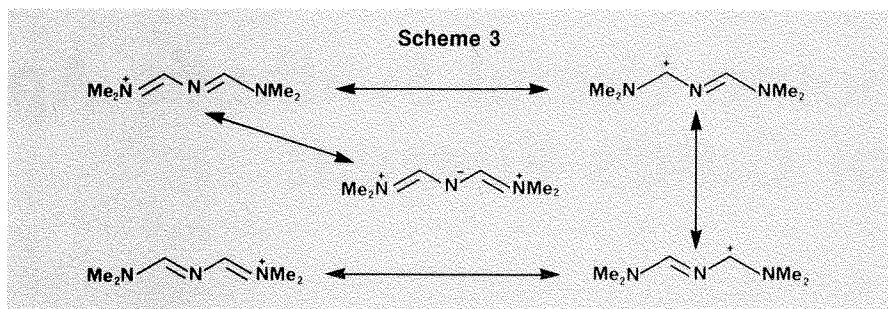


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Since some dinucleophiles had already been investigated by Gold<sup>3</sup> and Jutz,<sup>4</sup> we decided initially to study<sup>8</sup> some simple mononucleophiles such as amines, and anions derived from aryl methyl ketones and benzamides (Scheme 4). All these reactions proceed cleanly and in good yield to produce amidines, acylamidines and enamines which are useful and important materials in their own right.<sup>9</sup> Under these conditions, which normally employ NaOCH<sub>3</sub>/CH<sub>3</sub>OH, Gold's Reagent is functioning as a  $\beta$ -dimethylaminomethylenating agent. Apparently, what is happening in this situation is attack of a nucleophilic species at positions 1 or 3 of the reagent to form a tetrahedral intermediate which subsequently eliminates *N,N*-dimethylformamide (Scheme 5).

Danishefsky suggested that we follow up this study with a further investigation into the reaction of **2** with unsymmetrical ketones. Upon carrying out this work, we were surprised to learn that the reaction proceeded with complete regioselectivity to produce the least substituted enaminone (Scheme 6).<sup>10</sup> We believe that the high degree of regioselectivity results from a chair-like transition state in which gauche-type steric effects play a major factor. Since enaminones are important intermediates, this regioselective reaction may well prove useful to synthetic chemists.

In order to further extend the synthetic utility of Gold's Reagent, we decided to next examine anions derived from esters, lactones and *o*- or *p*-nitrotoluenes (Scheme 7).<sup>11</sup> These reactions also proved interesting since  $\beta$ -dimethylaminomethylenation was achieved. In addition, they are significant in that enamino lactones can be converted to  $\alpha$ -methylene lactones,<sup>12</sup> and *o*-nitrophenylenamines can be converted to indoles.<sup>13</sup>



Grignard reagents<sup>14</sup> were then treated with **2** to produce one-carbon-homologated aldehydes upon acid hydrolysis of the intermediates (Scheme 8). This method is general for aryl, benzyl and alkyl Grignard reagents and may well be the best method for the formylation of such carbanions. The reaction can be rationalized by the mechanism shown in Scheme 9.

More recently, we decided to extend our study of **2** beyond simple monofunctional nucleophiles to 1,4- and 1,5-dinucleophiles<sup>15</sup> which had not been previously examined by Gold (Scheme 10). In the reaction with *o*-phenylenediamines, *o*-aminophenols and *o*-hydroxyacetophenones, Gold's Reagent was found to function as a "one-atom lynchpin", whereas, in a similar reaction with anthranilic acid, **2** was found to function as a "two-atom lynchpin" to produce quinazolinones. The results are rationalized in Schemes 11 and 12.

Gold's Reagent has recently been used in the preparation of a chiral formamide from L-valinol *tert*-butyl ether. Reports of the use of this chiral auxiliary in the asymmetric syntheses of indole,<sup>16,17</sup> isoquinoline<sup>18-20</sup> and pyrrolidine<sup>21</sup> alkaloids have appeared.

### Conclusion

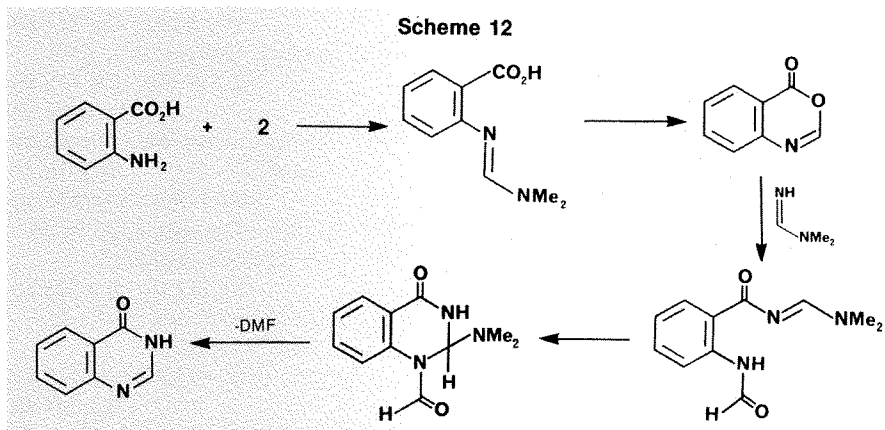
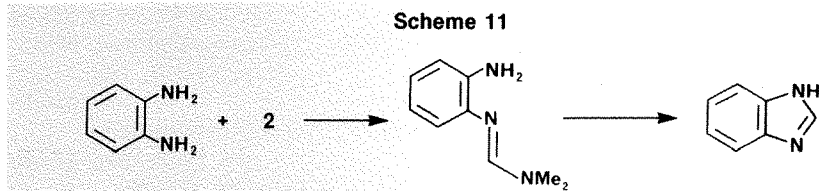
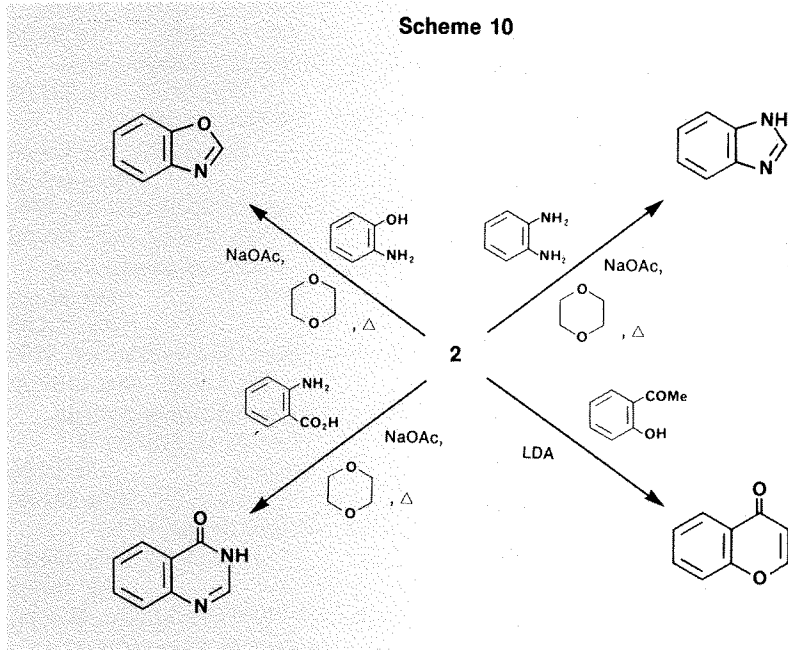
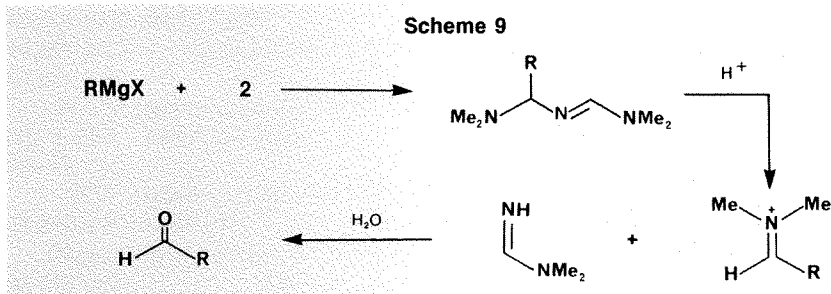
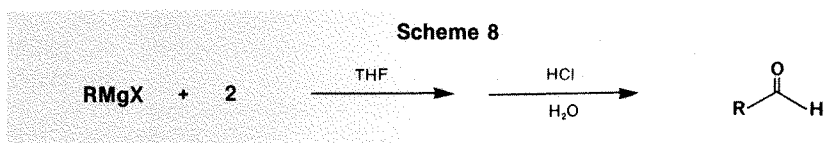
Although there are other reagents, such as the DMF acetals<sup>22</sup> and chloromethylene iminium salts,<sup>23</sup> which (in some cases) accomplish similar functions, Gold's Reagent has some distinct advantages. It is a well defined, stable and preformed salt which reacts with a variety of nucleophiles cleanly under slightly basic to basic conditions with significant regioselective control. We therefore consider Gold's Reagent to be an efficient, economical and clean alternative to analogous reagents. We believe that we have only begun to scratch the surface of synthetic methodology available through the reactions of this interesting substance.

### Acknowledgements

The author would like to thank the Petroleum Research Fund, The Research Corporation, The National Science Foundation and the University of Central Florida Division of Sponsored Research for support of this work. In addition, the significant contributions by numerous students at the University of Central Florida are acknowledged.

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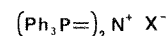


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#### About the Author

John Gupton received the B.Sc. degree from the Virginia Military Institute in 1967 and the M.S. degree from Georgia Tech. in 1969. After a 3-year tour of service in the U.S. Air Force he received his Ph.D. degree from Georgia Tech. in 1975 under the direction of Dr. Drury Caine. He spent 3½ years in the Agricultural Division of CIBA-GEIGY Corporation prior to joining the University of Central Florida in 1978. His research interests include new synthetic applications of vinylogous iminium salts, new methods for the incorporation of fluoroalkyl groups into organic molecules and novel reactions of HMPA.

## Organometallics

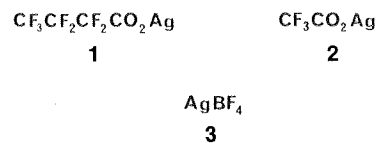


Bis(triphenylphosphoranylidene)ammonium acetate (PPN acetate) catalyzes the monosubstitution of triruthenium dodecacarbonyl with triphenylphosphine.<sup>1</sup> It also reacts with triruthenium dodecacarbonyl to form a trinuclear cluster.<sup>2</sup>

Bis(triphenylphosphoranylidene)ammonium nitrite (PPN nitrite) converts metal carbonyls to nitrosyl carbonyl complexes, in high yields with no side products.<sup>3</sup>

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#### Versatile Silver Salts



Silver heptafluorobutyrate (**1**) and silver trifluoroacetate (**2**) are both used for the preparation of heptafluoro-2-nitrosopropane and 1-chlorohexafluoro-2-nitrosopropane, avoiding the use of nitrosyl fluoride.<sup>1</sup> They also react with halobis(trifluoromethyl)phosphine to give the corresponding carboxylatobis(trifluoromethyl)phosphines.<sup>2</sup>

Silver heptafluorobutyrate and silver tetrafluoroborate (**3**) catalyze the formation of tricyclanone from 3-diazocamphor.<sup>3</sup>

Mixtures of **1** and lanthanide (fod)<sub>3</sub> act as binuclear shift reagents for alkenes.<sup>4</sup>

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