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Enhanced Reactivity in Homogeneous Gold Catalysis through Hydrogen Bonding

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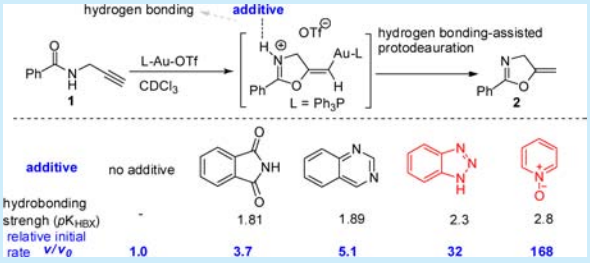
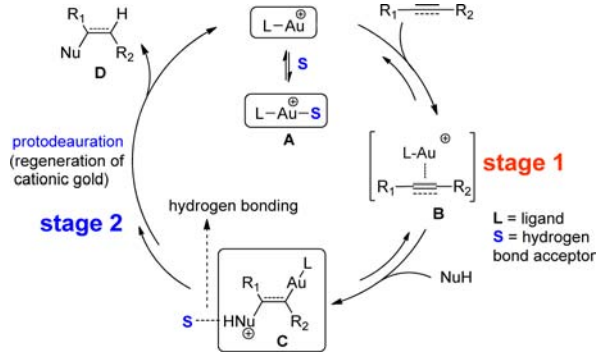
Supporting Information

ABSTRACT: Additives that are good hydrogen-bond acceptors increase the efficiency of gold-catalyzed reactions in those instances where protodeauration is the rate-determining step. The efficiency of additives capable of hydrogen-bonding-assisted protodeauration correlated with their standing in a scale of hydrogen bonding basicity (measured by pK_{BHX}). All additives used in the study are commercially available.



Gold catalysis is a landmark addition to the field of organic synthesis.[1] It is well established that most gold-catalyzed reactions go through two major stages (Scheme 1).[2] In stage 1

Scheme 1. Stages in the Gold Catalytic Cycle



(from L-Au$^+$ to **C**), a nucleophile attacks a gold alkyne/alkene μ2-complex **B** to generate a charged gold intermediate **C**. In stage 2, **C** is converted to product with concomitant regeneration of the cationic gold species via protodeauration.[3] If **C** contains a relatively basic heteroatom (e.g., nitrogen), it may be reluctant to relinquish its proton. A positively charged intermediate **C** is aversed to undergo protodeauration because its positive charge is a deterrent for an incoming proton. Indeed, many charged vinyl gold species have been isolated (e.g., **Au-2** in Figure 1) because they have shown high resistance toward protodeauration.[4] The turnover limiting stage for many gold-catalyzed reactions actually occurs in the protodeauration stage (stage 2).[5] We now report a new strategy to enhance the efficacy of gold-catalyzed reactions through hydrogen-bonding assisted protodeauration using additives chosen for their pK_{BHX} (hydrogen-bond basicity)[6] rather than for their pK_a.

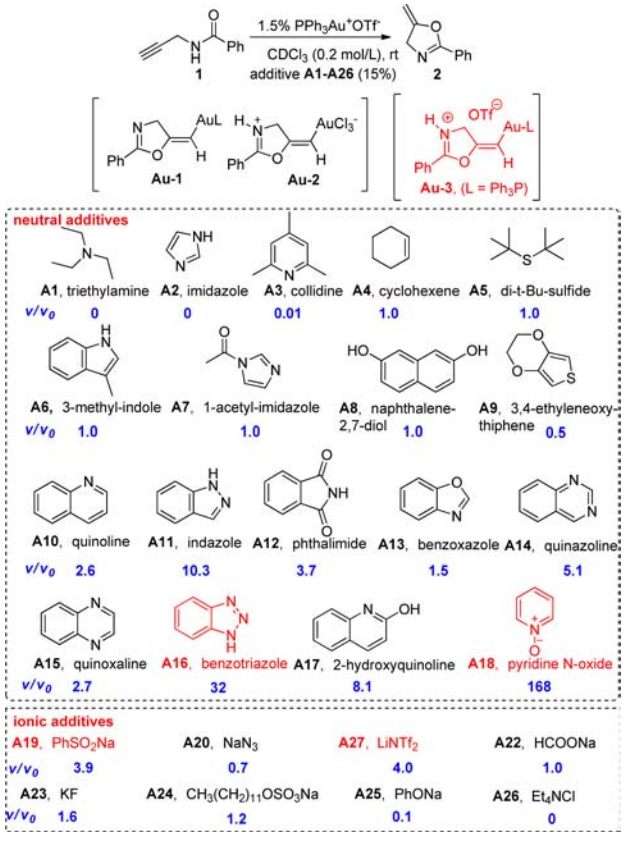


Figure 1. Survey of additive effects in the cyclization of **1**.

Addition of a relatively strong base has a deleterious effect in the protodeauration of **C** (Scheme 1). Although a base will

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remove the proton in **C**, it will also quench any acid in the system, and by doing so it will inhibit protodeauration.

We asked ourselves if a hydrogen-bond acceptor with low basicity could be a better alternative (**S** in Scheme 1). The nonbonding orbital of **S** will partially transfer its charge to the antibonding σ^* orbital of **C**.[7] This effect will reduce the positive charge on **C** and cause the hydrogen bond acceptor to function as a proton shuttle, thus facilitating protodeauration. This concept is similar to general base catalysis,[8] with **S** acting as a general base. General base catalysis is a common occurrence in biological systems where strong bases are not tolerated and where deprotonation or proton transfer is mediated by weak bases though hydrogen-bonding interaction.[9]

In gold catalysis, the role of a hydrogen bond acceptor (**S** in Scheme 1) is more complex than that of a general base. Because **S** is aurophilic to some extent, it competes with an alkyne/alkene starting material in their complexation with cationic gold (Scheme 1). Hence, with regard to stage 1, **S** could be considered a reversible inhibitor. Only if the acceleration effect of **S** outweighs its inhibitory effect, the effect of S in the overall reaction will be positive. Thus, **S** will be useful in gold catalysis only when protodeauration is the rate-determining step.

To implement our proposed tactic, we screened a diverse group of additives using a well-studied gold-catalyzed reaction in which stage 2 (protodeauration) is known to be the slow step.[5] The reaction we chose was the gold-catalyzed cyclization of propargyl amide **1** to oxazole **2**[10] because its key vinyl gold intermediate (**Au-1**, L = IPr) had been identified by the Hashmi group in the case of gold(I)[10b,11] and by Ahn[4a] in the case of gold(III) (**Au-2**) (Figure 1). Based on those studies, we proposed that intermediate **Au-3** is equivalent to **C** in Scheme 1. We measured the initial reaction rate in the absence of an additive (v_0), and the initial reaction rate (v) in the presence of various additives and then calculated the ratio v/v_0 for each additive. The data shown in Figure 1 indicated that basic additives completely inhibited the reaction [e.g., **A1** (Et_3N, pK_{aH} = 9.0), **A2** (imidazole, pK_{aH} = 7.1)]. These results are not surprising because stronger bases ought to inhibit the protodeauration step (stage 2 in Figure 1).

Additives that were less basic than collidine (**A3**) did not inhibit the reaction, but most of them (e.g., **A4-A8**: alkene, phenol, sulfide, indole, and acetyl imidazole) had no effect on the kinetics of the reaction (v/v_0 = 1). We were pleased though when *N*-heterocycles, such as benzotriazole (**A16**, v/v_0 = 32), indazole (**A11**, v/v_0 = 10.3), and quinazoline (**A14**, v/v_0 = 5.1) showed dramatic acceleration effects and were astounded when pyridine *N*-oxide (**A18**) increased the reaction rate 168 times. The only way that benzotriazole (**A16**), a good hydrogen bond acceptor, could have accelerated the protodeauration of **Au-3** is through hydrogen bonding. Indeed, **A16** cannot accelerate the protodeauration of a neutral vinyl gold complex (see the Supporting Information).

Although it is commonly assumed that the relative hydrogen-bond strength of an organic compound bears a simple correlation with its basicity (pK_{aH}), this assumption holds true only for structurally related compounds in a series.[7] As shown in Figure 2, the lack of a discernible pattern in the graph of $\ln(v/v_0)$ (from our survey in Figure 1) vs pK_{aH} underscores the fact that the pK_{aH} of additives is not a good forecast of their usefulness.

In 2009, Laurence and co-workers reported a comprehensive database of hydrogen-bond basicity (measured by pK_{BHX}).[6] Using Laurence's data, we were able to establish a quantitative

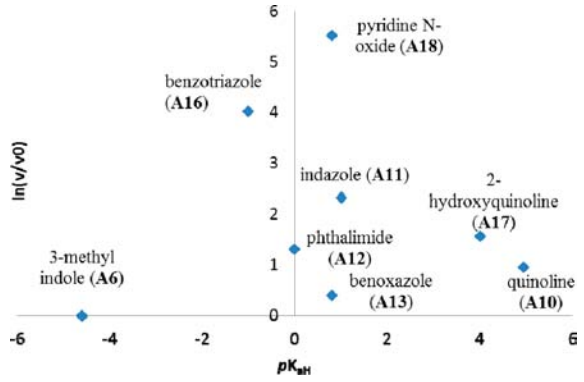

Figure 2. Activity of additives [measured by $\ln(v/v_0)$] vs their basicity (pK_{aH}).

correlation between the efficiency of an additive and its hydrogen-bond basicity (Figure 3). The correlation in Figure 3

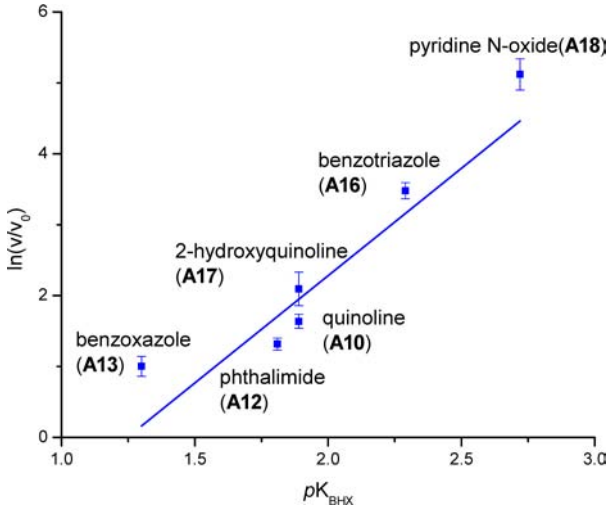

Figure 3. Activity of additives [measured by $\ln(v/v_0)$] vs their hydrogen-bond basicity (measured by pK_{BHX}).[12]

not only offers strong experimental support for the role of hydrogen bonding but it also serves as a practical guide for the selection of additives. Using Laurence's database as guide we selected other compounds that were good hydrogen bond acceptors (pK_{BHX} > 2.6) and had low basicity (pK_{aH} < 4) and found new hits such as DMPU, HMPA, and trimethylphosphine oxide (v/v_0 = 18.7, 23.9, 30.2 respectively). All these were excellent accelerators for the cyclization of **1** even though their structures were quite different.

We also screened ionic additives (**A19**−**A26**) with different basicities and found that they too enhanced the kinetics of the reaction although their effects were moderate. Many ionic salts are also good hydrogen bonding acceptors[6] but because no comprehensive pK_{BHX} data for ionic compounds is available, we could not correlate the reactivity of ionic additives with their pK_{BHX}.

To increase our understanding of hydrogen bond effects we explored other gold-catalyzed reactions (Scheme 2). First we investigated the intermolecular hydroamination of alkynes.[5] As shown in Scheme 2a, a kinetic enhancement was observed in the presence of additives that had proven effective in the cyclization of **1** (e.g., pyridine *N*-oxide, benzotriazole), but the enhancement was less dramatic. We attributed this result to the

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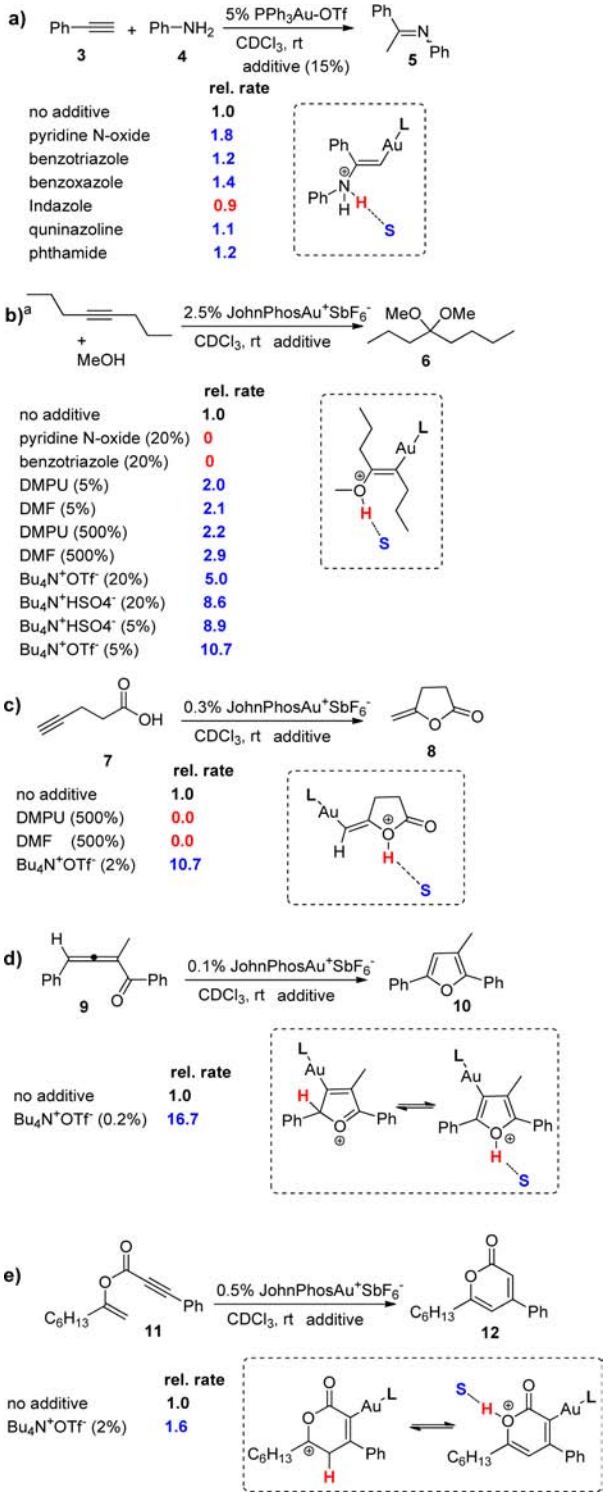
Scheme 2. Additive Effects on Various Gold-Catalyzed Reactions (S = Hydrogen Bond Acceptor)[a]



[a]Part of **6** was hydrolyzed to ketone by trace water.

fact that the starting material (amine) in the hydroamination is in itself a relatively good proton acceptor and also a good hydrogen bond acceptor.

We also investigated the intermolecular addition of methanol to alkyne (Scheme 2b). We found that hydrogen bond acceptors with relatively high gold affinity (pyridine *N*-oxide, benzotriazole) inhibit or slow down the reaction. This result was not surprising because stage 1 is the slow or rate-determining step in this intermolecular reaction in which the nucleophile (MeOH) is weak compared to an amine. As expected, hydrogen bond acceptors with lower gold affinity (e.g., DMPU, DMF)[13] enhanced the rate of reaction (Scheme 2b), and ionic hydrogen bond acceptors (e.g., $Bu_4N^+OTf^-$) performed significantly better, possibly because of their even lower affinity toward cationic gold.

Although the pK_{BHX} of $Bu_4N^+OTf^-$ was not reported in Laurence's database, the pK_{BHX} values of related salts, such as $Bu_4N^+X^-$ (X = Cl, I), have been tabulated (pK_{BHX} = 2.8 and 4.2, respectively).[6] These values demonstrate their good hydrogen-bond acceptor properties. Given its similarities with $Bu_4N^+X^-$, $Bu_4N^+OTf^-$ should also be a good hydrogen bond acceptor, but the latter has the added advantage of its low basicity and low affinity toward gold. We found that $Bu_4N^+OTf^-$ also enhanced the reaction rates of other reactions like cycloisomerization of allenone **9**,[14] cyclization of 4-pentynoic acid **7**,[15] and synthesis of α-pyrone[16] (Scheme 2c–e) substantially. Neutral hydrogen bond acceptors were less effective in those reactions, most likely because of their relatively high affinity toward cationic gold.

Other research groups reported that certain compounds improved the chemical yields in selected gold-catalyzed reactions.[17] One notable example is the $Ph_3PAu^+OTf^-$ benzotriazole complex reported by Shi and co-workers;[18] this complex performed better than $Ph_3PAu^+OTf^-$ in a number of transformations, such as the Hashmi phenol synthesis or the rearrangement of propargyl esters. Our hydrogen bonding argument not only accounts for the $Ph_3PAu^+OTf^-$ benzotriazole complex success but also offers a guide for the selection of other suitable hydrogen bond acceptors.

In summary, an ideal hydrogen bond acceptor additive should have (i) high hydrogen bonding basicity, (ii) low basicity, and (iii) low affinity toward cationic gold. Additives with high hydrogen bonding basicity often show high affinity toward cationic gold. In general, if stage 1 of a given reaction is very fast (as in the cyclization of **1**), a good hydrogen bond acceptor with relatively high gold affinity (e.g., benzotriazole) will be useful because, even if it does slow down stage 1, its ability to speed up stage 2 will cause the overall reaction to be faster (because stage 1 is faster than stage 2). But if stage 1 in the target reaction is relatively slow, then the additive's high affinity toward cationic gold may slow down or inhibit the reaction. In this case, a hydrogen bond acceptor with a relatively low affinity toward cationic gold (e.g., DMPU, $Bu_4N^+OTf^-$) will be useful. Hence, the overall effectiveness of a hydrogen bond acceptor will depend on the balance between the two effects. All additives used in the study are commercially available compounds, a clear advantage to synthetic chemists.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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