

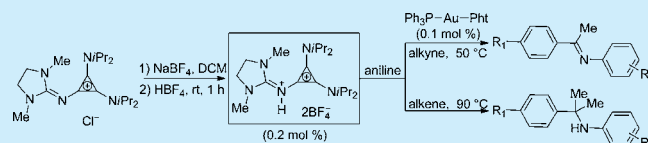
Expanding the Forefront of Strong Organic Brønsted Acids: Proton-Catalyzed Hydroamination of Unactivated Alkenes and Activation of Au(I) for Alkyne Hydroamination

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S Supporting Information

ABSTRACT: The synthesis of a solid, bench-stable, strong organic Brønsted acid with a computed pK_a of 0.9 is reported. An X-ray crystal structure and DFT calculations are provided which offer insight into the bonding of this acid. The application of this strong organic Brønsted acid as a catalyst for the intermolecular hydroamination of unactivated alkenes and as an activator for Au(I)-catalyzed alkyne hydroamination with anilines is described.



The importance of Brønsted acids would be hard to understate given their importance in countless biological processes as well as their use in industrial manufacturing and experimental laboratories worldwide. In this vein, with the advent of the field of organocatalysis in recent years, the development and use of metal-free, strong Brønsted acids has had an influential role, and accordingly, efforts on this front continue to mount at a rapid pace.¹ Most notably, there have been a number of exceptional applications using nonchiral² and/or chiral strong Brønsted acids, such as the pentafluorophenylbis-(triflyl)methane, polystyrene-bound tetrafluorophenylbis-(triflyl)methane,³ and *N*-triflylphosphoramidate (NTPA) catalysts of Yamamoto⁴ and disulfonimide (BINBAM) catalysts of List,⁵ to name but a handful.

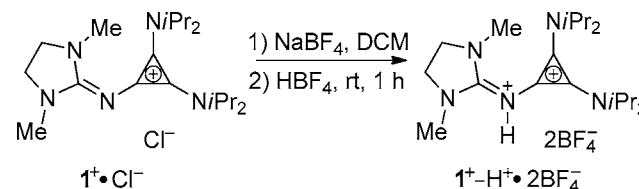
While these works are impressive, unmet challenges remain with respect to the advancement of strong Brønsted acids in catalysis and synthesis; this is particularly evident for catalytic C–N bond formation. Lacking, in particular, are solid, bench-stable, strong organic Brønsted acids that, in addition to being inexpensive or easily prepared, serve the paramount role(s) of functioning as catalysts, precatalysts, activators, or other foreseeable useful tasks. Accordingly, the design and synthesis of new strong organic Brønsted acids offers the promising potential of achieving reactivity that is unavailable with known Brønsted acids or, at the very least, provides complementary patterns of reactivity which are still needed.

From a more fundamental perspective, it is interesting to note that, despite a general interest in developing new strong organic Brønsted acids in recent years, H-bonding has been a debated topic for almost a century that continues to garner appreciable attention.⁶ The origin of this controversy can be traced back to the seminal works of Nobel laureate Linus Pauling and Gilbert Newton Lewis, who in the early 1900s held opposing views on the subject, Pauling arguing in favor of the electrostatic “dipole–dipole” as opposed to Lewis’s view of “partial covalent” character of H-bonding. Consequently, the advancement of new, strong organic Brønsted acids not only offers the attractive prospect of

cultivating a more lucid understanding of H-bonding but also brings with it the promise of developing a novel H-bonding catalyst.

Mindful of the above-mentioned limitations and having a longstanding interest in Brønsted acid catalysis,⁷ we were intrigued by the potential of protonating our recently reported pnictogen based *N*-centered class of phase-transfer catalysts (PTCs)⁸ (e.g., $1 \cdot Cl^-$, Scheme 1) as this action would serve the

Scheme 1. Synthesis of Dication $1^+ \cdot H^+ \cdot 2BF_4^-$



trifold role: (1) a dicationic conjugate acid $1^+ \cdot H^+$ would be generated that foreseeably could be a super acid or at the very least a strong organic Brønsted acid, (2) dication $1^+ \cdot H^+$ would offer the prospect of gaining insight into H-bonding, and (3) conceivably, dication $1^+ \cdot H^+$ would have synthetic utility. Accordingly, we report herein the synthesis, X-ray structure, hybrid density functional theory (DFT) calculations, and use of dication $1^+ \cdot H^+$ as a strong Brønsted acid catalyst (loadings 0.2 mol %) for intermolecular hydroamination of unactivated alkenes and as an activator for Au(I)-catalyzed alkyne hydroamination with anilines.

At the outset, with the aim of preparing the protonated derivative of $1^+ \cdot H^+$ from reported $1^+ \cdot Cl^-$, several factors, such as the need for $1^+ \cdot H^+$ to be a crystalline salt that was easy to handle and accessible without undue experimental manipulation, were considered. Attentive to these criteria, initial studies led to the

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finding of the bench-stable salt, $1^+-H^+ \cdot 2BF_4^-$, which could be prepared in gram quantities from $1^+ \cdot Cl^-$ by $NaBF_4$ counterion exchange, followed by protonation using HBF_4 (Scheme 1). An X-ray structure was then obtained from a single crystal to better understand the structure and bonding in $1^+-H^+ \cdot 2BF_4^-$.

Notably, the X-ray structure revealed a number of striking features among which was the presence of a H-bonded water molecule to the protonated N(1) nitrogen residing at a distance of 1.83 Å. A restricted optimization calculation at the B3LYP/LanL2DZ level of theory in which all of the heavy atoms were frozen and the hydrogens left unconstrained using the X-ray coordinates of $1^+-H^+ \cdot 2BF_4^-$ as a starting point to remove any spatial artifacts resulting from X-ray based assignment of hydrogen locations provided a very similar structure in all respects (Figure 1). Apparent from this structure was that the

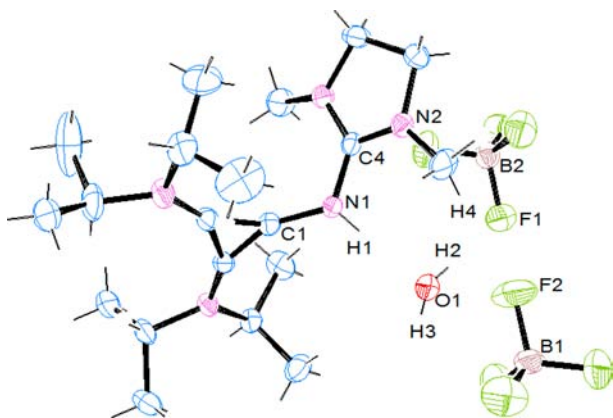


Figure 1. X-ray structure of $1^+-H^+ \cdot 2BF_4^- \cdot H_2O$.

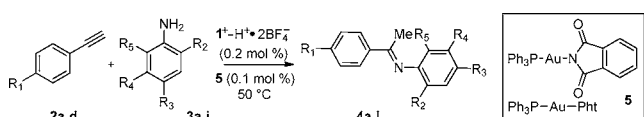
$N(1)^+-H^+-O(1)$ contact exhibits a characteristic quantum theory of atoms in molecules (QTAIM) bond critical point (BCP) with density $\rho = 0.05$ au and Laplacian value $\nabla^2\rho_{bcp} = 0.038$ au, thus typifying this interaction as a moderate strength H-bond (see the Supporting Information). Meanwhile a natural bond orbital (NBO) analysis of the donor–acceptor nature of this interaction, uncovered that there was significant charge transfer from one oxygen lone pair into the antibonding σ^* -orbital of the N^+-H bond ($E_{NBO} = 40.1$ kcal/mol), hence supporting a noticeable degree of fractional chemical bonding or, that is, charge-transfer-based “partial covalent” H-bonding character. The H-bonding/proton-donor ability of N(1) can be traced not only to the electron deficiency of dication 1^+-H^+ (see the Supporting Information for ESP isosurface) but also to the considerable s-character of this nitrogen as judged from the NBO computed $s^1p^{2.2}$ hybridization of N(1) and X-ray-determined C(1)–N(1)–C(4) metric of 122.3° .

Conspicuous as well was the displacement of the two BF_4^- counteranions away from the aromatic cyclopropenium ring toward the imidazolium hemisphere of 1^+-H^+ , likely as a result of the known donor–donor ion pair strain associated with cyclopropenium ring systems. One of the BF_4^- anions resides toward the lower face of the complex, forming an H-bond with H(2) of the water molecule (distance = 1.83 Å) and two hydrogens of the imidazolium unit, based on the presence of BCPs ($\rho = 0.004, 0.009$ au) and the computed noncovalent interaction (NCI) isosurface. The second BF_4^- anion is located further from the parent dication, albeit visible is an apparent H-bond contact with H(3) of the water molecule (distance = 1.90

Å) and one of the moderately acidic methyl hydrogens of the N(2)–Me group ($\rho_{BCP} = 0.009$).

Having structural insight, the acidity of $1^+-H^+ \cdot 2BF_4^-$ was computed to aid our selection of potential reactions for applying $1^+-H^+ \cdot 2BF_4^-$. To this end, the calculated relative pK_a of 1^+-H^+ at the B3LYP/6-31G+(d)//SMD/M06-2x/6-311G++(2df,2p) level of theory using the IEFPCM solvation model (acetonitrile, $\epsilon = 35.5$) was computed to be 0.9 (see the Supporting Information for details). Meanwhile, the gas-phase proton affinity (PA) of 1^+ [B3LYP/6-31G+(d)//M062x/6-311G++(2df,2p)], considering thermal corrections computed at the B3LYP/6-31G+(d) level of theory, was determined to be 178.8 kcal/mol. At that stage, with insight into the strong Brønsted acidity of $1^+-H^+ \cdot 2BF_4^-$ and mindful of (1) the timely significance of alkyne/alkene hydroamination as a strategy for preparing nitrogen-containing molecules⁹ and (2) current interest in group 11 gold-catalyzed reactions, we turned to the use of 1^+-H^+ as an activator for Au(I)-catalyzed alkyne/alkene hydroamination.

In this respect, it is noteworthy that the majority of homogeneous gold-catalyzed processes reported to date have relied on the use of silver-mediated activation of gold(I) precatalyst by halogen abstraction. The use of silver activators, however, is not without shortcomings as silver salts and their byproducts may negatively impact a reaction by forming various Au and Ag adducts which are catalytically inactive. Moreover, silver salts often are light sensitive, relatively expensive, unavailable commercially, difficult to prepare, and/or have poor solubility. To address these limitations, the use of a strong organic Brønsted acids to generate catalytically active Au(I) species via protonolysis has emerged as a promising complement to silver-mediated activation. Accordingly, the use of $1^+-H^+ \cdot 2BF_4^-$ as an activator for Au(I)-catalyzed alkyne hydroamination using gold precatalyst **5** was envisioned. To this end, we were pleased to find that $1^+-H^+ \cdot 2BF_4^-$ (0.2 mol %) under mild conditions served as a competent activator of gold precatalyst **5** (0.1 mol %) leading to N–C bond forming addition of aniline **3a** to alkyne **2a** to afford imine **4a** in 22% yield (Table 1, entry 1), while when the same conditions were applied for 48 h the yield increased to 60%. Encouraged by this initial finding, we set out to further explore the scope of this reaction by reacting a range of substituted alkynes and amines. Notably, the reaction yield increased to 87% with resonance-donating electron-withdrawing 4-bromo substituent aniline **3b**, while the use of **3c** having a more electron-withdrawing and less resonance donating 4-fluoro substituent led to a decrease in yield (Table 1, entries 2 and 3). Intrigued by this finding, we then subjected 2,5-dichloroaniline (**3d**) to the reaction conditions to afford imine **4d** in high yield, 95%, after only 4 h (Table 1, entry 4). Meanwhile, when **3e** having an electron-withdrawing 4-nitro substituent was used, **4e** was obtained in 19% yield (Table 1, entry 5). Moreover, longer reaction times did not improve the yield, presumably due to poisoning of the in situ formed Au(I) catalyst. On the other hand, products **4f** and **4g** were obtained in low yield from the reactions of electron-rich 4-alkyl-substituted anilines **3f** and **3g** (Table 1, entries 6 and 7). This reduced yield is thought to arise from greater competitive binding of the Au(I) catalyst by electron-rich anilines, which in turn diminishes alkyne activation by gold coordination and ultimately slows the rate of aniline addition. The subsequent use of 2-ethylaniline (**3h**), which was anticipated to afford better yields, as Au(I)–aniline association should be less favorable due to the presence of an *o*-alkyl group, afforded product **4h** in moderate yield after 24 h (Table 1, entry 8).

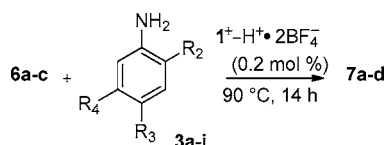
Table 1. Au(I)-Catalyzed Alkyne Hydroamination Using Brønsted Acid $1^+-H^+ \cdot 2BF_4^-$ as an Activator

entry	nucleophile					time (h)	yield ^a (%)			
	R ₂	R ₃	R ₄	R ₅						
1	2a	H	3a	H	H	H	24	4a	22 ^{b,c}	
2	2a	H	3b	H	Br	H	H	24	4b	87
3	2a	H	3c	H	F	H	H	24	4c	57
4	2a	H	3d	Cl	H	Cl	H	4	4d	95
5	2a	H	3e	H	NO ₂	H	H	4	4e	19
6	2a	H	3f	H	C ₂ H ₅	H	H	24	4f	11
7	2a	H	3g	H	C ₄ H ₉	H	H	24	4g	11
8	2a	H	3h	C ₂ H ₅	H	H	H	24	4h	49
9	2a	H	3i	Me	Me	H	Me	24	4i	50
10	2b	OMe	3a	H	H	H	H	24	4j	95
11	2c	Me	3a	H	H	H	H	24	4k	47
12	2d	F	3a	H	H	H	H	4	4l	46

^aYields of isolated products after flash chromatography. ^bYield increased to 60% after 48 h. ^cReaction conversion after 48 h was insignificant (<1%) based on ¹H NMR when the Brønsted acid, metal, or Brønsted acid–metal combination was excluded.

To further investigate the effect of steric interactions on the reaction, 2,4,6-trimethylaniline (**3i**) was subjected to the reaction conditions to generate **4i** in a moderate yield (Table 1, entry 9). Switching to the activated substrate, 4-ethynylanisole (**2b**), resulted in a dramatic enhancement in reaction yield (95%) (Table 1, entry 10). Furthermore, the reaction of the 4-fluorophenylacetylene and 4-methylphenylacetylene substrates **2c** and **2d** afforded products in moderate yield, which was somewhat interesting considering the electronic differences existing between these substrates (Table 1, entries 11 and 12).

Having demonstrated the catalytic ability of our Au(I)/ $1^+-H^+ \cdot 2BF_4^-$ system for alkyne hydroamination, the more challenging reaction of alkene hydroamination was undertaken. In this respect, it was of particular interest to see if the unique reactivity associated with our Au(I)/ $1^+-H^+ \cdot 2BF_4^-$ catalyst would allow for the addition of anilines to unactivated alkenes. To our delight, the reaction of α -methylstyrene (**6a**) with aniline **3b** and catalytic $1^+-H^+ \cdot 2BF_4^-$ (0.2 mol %) and **5** (0.1 mol %) afforded Markovnikov addition product **7a** in 86% yield. Nevertheless, a careful analysis of hydroamination background rates revealed that strong Brønsted acid $1^+-H^+ \cdot 2BF_4^-$ (0.2 mol %) in the absence of gold effectively catalyzed alkene hydroamination with comparable yield (Table 1, entry 1). Though serendipitous, this result was nonetheless remarkable given the low loadings of Brønsted acid $1^+-H^+ \cdot 2BF_4^-$ relative to the larger loadings (e.g., 1–5 mol %) employed for the intermolecular hydroamination of unactivated alkenes with anilines reported to date.¹⁰ To briefly establish the scope of this process, a selection of unactivated alkenes were then subjected to the catalytic action of $1^+-H^+ \cdot 2BF_4^-$. In this regard, the reaction of **6a** with aniline **3a** led to a dramatic decrease in yield (Table 2, entry 2). On the other hand, **7c** was isolated in moderate 59% yield from the hydroamination of styrene with **3d** (Table 2, entry 3). The reaction of anilines **3d** or **3b** with bicyclo[2.2.1]hept-2-ene (**6c**) as a substrate employing the same

Table 2. Au(I)-Catalyzed Alkene Hydroamination Using Brønsted Acid $1^+-H^+ \cdot 2BF_4^-$ as an Activator

entry	olefin	nucleophile	product	yield ^a (%)
1	6a	3b	7a	84 ^{b,c}
2	6a	3a	7b	17
3	6b	3d	7c	59
4	6c	3d	7d	92
5	6c	3b	7e	93

^aYields of isolated products after flash chromatography. ^bBrønsted acid, $1^+-H^+ \cdot 2BF_4^-$, (0.2 mol %), and **5** (0.1 mol %) afforded a comparable yield of 86%. ^cNo conversion was observed using only **5** (0.1 mol %) or when both $1^+-H^+ \cdot 2BF_4^-$ and **5** were excluded.

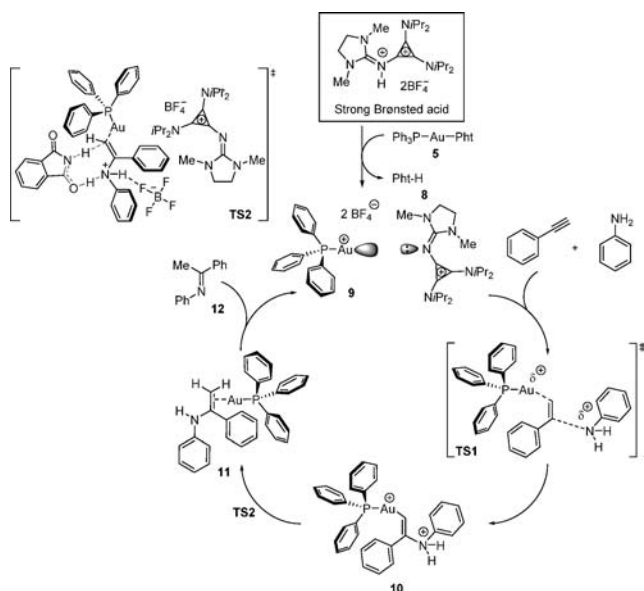
reaction conditions provided **7d** and **7e** in 92% and 93% yield, respectively (Table 2, entries 4 and 5).

The proposed mechanisms of these alkyne and alkene hydroamination reactions warrant mention as they likely share parallels with many previous mechanistic posits while possessing a number of key differences. The mechanism for alkene hydroamination with catalytic $1^+-H^+ \cdot 2BF_4^-$ is believed to be intimately tied to the formation of a continuum of highly separated ion pairs composed of weakly associating anionic BF_4^- , cationic 1^+ , and acidic protonated anilinium moieties which are strong H^+ donors. In this respect, it is notable that Bergman et al. have previously suggested that decreasing counteranion association enhances anilinium acidity.¹¹ Importantly, this factor was critical for facilitating alkene protonation and hydroamination with anilines in the authors' report.

As for alkyne hydroamination, it is thought that the catalytic cycle for this process initiates with protonolysis of the Au–N bond of precatalyst **5** by strong Brønsted acid $1^+-H^+ \cdot 2BF_4^-$ to generate phthalimide **8** and Lewis acidic gold(I) species **9**. At that stage, having served its most salient role, $1^+-H^+ \cdot 2BF_4^-$ shifts from being a strong Brønsted acid to that of a bulky lipophilic cation/(weakly associated) $1^+ \cdot BF_4^-$ ion pair. Functioning in a second role, the diffuse cation 1^+ of ion pair $1^+ \cdot BF_4^-$ then

conceivably acts as an antagonist of Au(I) counterion association by sequestering BF_4^- away from the Au(I) metal center, thus enhancing the innate reactivity of the electron-deficient gold(I) catalyst and freeing it for alkyne binding. Regardless, the hydroamination of an activated Au(I)-alkyne π -complex by aniline via TS1 subsequently ensues to provide transient addition product 10. Byproduct phthalimide 8, BF_4^- , a molecule of water or potentially even $\text{I}^+\cdot\text{BF}_4^-$, then act as a shuttle for proton transfer to provide the Au(I) coordinated enamine 11 after protodeauration. While it is too early to diagnostically confirm which of the above scenarios is more favorable, we tentatively propose that phthalimide 8 mediates proton transfer through TS2 as depicted in Scheme 2. Subsequently, the catalytic cycle

Scheme 2. Proposed $\text{I}^+\text{-H}^+\cdot 2\text{BF}_4^-$ and Au(I)-Catalyzed Cycle for Alkyne Hydroamination



completes with dissociation of the Au(I) catalyst and enamine tautomerization to afford imine 12. Ongoing mechanistic studies are underway to gain insight into these hydroamination reactions, and the findings of this work, which are anticipated to provide valuable understanding for improving these processes, will be reported in due course.

To summarize, we have reported the synthesis of a solid, bench-stable, strong organic Brønsted acid which can be prepared in gram quantities. X-ray structural data and DFT calculations offering insight into the bonding of this strong organic Brønsted are also provided. The use of this Brønsted acid as catalyst for the hydroamination of unactivated alkenes and as an activator for Au(I)-catalyzed alkyne hydroamination with anilines is described.

■ ASSOCIATED CONTENT

☞ Supporting Information

Experimental procedure, spectroscopic data for all new compounds, crystallographic data (CIF), and computational details for $\text{I}^+\text{-H}^+\cdot 2\text{BF}_4^-$. 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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