## A Simple Halide and Silver-Free Synthesis of Echavarren's Catalyst Directly from Gold Powder

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An expedient procedure is reported for the preparation of the synthetically valuable Au(I) complex [Au(MeCN)(P^{t}Bu$_2$C$_6$H$_4$Ph-2)][BF$_4$] (Echavarren's catalyst) directly from gold powder using [NO][BF$_4$] in acetonitrile. The synthetic method obviates the potential presence of silver or halide impurities that follow from the tedious conventional synthesis, and have otherwise been shown to moderate catalyst performance.

Introduction

In recent decades there has been a rapid growth in the development of both Au(I) and Au(III) catalysed reactions.[1] With regard to Au(I) systems it was work reported by Teles and co-workers[2] describing the Au(I) catalysed nucleophilic additions to alkynes, and subsequent work by Tanaka[3] employing the same catalyst for alkyne hydration that sparked a marked interest in the area (Scheme 1).
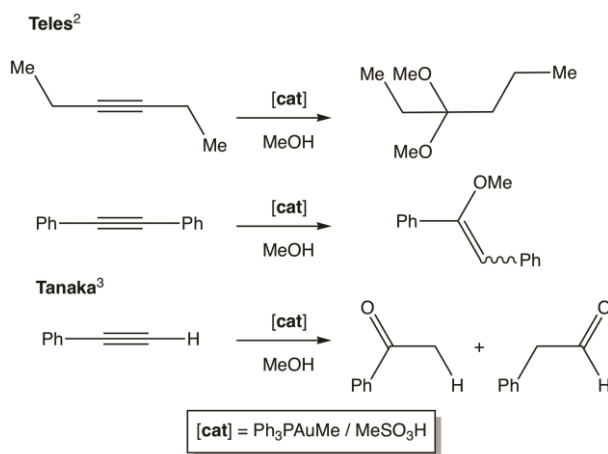
Scheme 1. Au(I) activation of alkyne precursors toward nucleophilic attack by methanol.

Building on this work, the activation of $\pi\pi$ bonds by Au(I) has allowed for the development of a diverse range of organic functionalisations via robust protocols. For example, Au(I) catalysed cyclizations and cycloadditions reactions now allow for the rapid introduction of molecular complexity into organic frameworks from readily available

precursors.[1,4-5] Foremost amongst gold mediators has been Echavarren's catalyst [Au(NCMe)(P^{t}Bu$_2$C$_6$H$_4$Ph-2)][SbF$_6$], [**1**]SbF$_6$, as exemplified by the facile synthesis of benzo[b]furans (**2**) via intramolecular cyclisation of furan-ynes **3**, under mild conditions (Scheme 2).[6]
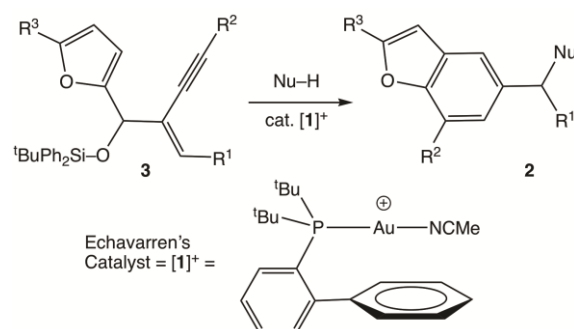
Scheme 2. Au(I) catalysed transformation of furan-ynes to yield substituted benzofurans.

The conventional synthesis of Echavarren's catalyst and related [Au(NCMe)(PR$_3$)]X complexes (X = non-coordinating anion) mediators involves (i) Oxidation of gold metal to tetrachloroauric acid by digestion in *aqua regia* which is then removed by distillation; (ii) Alcoholic reduction in the presence of a thioether to provide [AuCl(SR$_2$)] (SR$_2$ = SMe$_2$, tetrahydrothiophene); (iii) Substitution of the labile thioether by the phosphine of choice to afford [AuCl(PR$_3$)] and finally (iv) Chloride abstraction by a silver salt of the desired non coordinating anion 'X$^-$' in acetonitrile (Scheme 3). This final step calls for highly accurate stoichiometry that is achieved with difficulty for small scale preparations, though less problematic for the large scale syntheses performed by commercial suppliers.[7] Any deficiency in halide abstraction leaves residual chloride precursor whilst excess results in contamination with silver salts that with time deteriorate to colloidal silver in either case remaining present and potentially interfering with the desired catalytic process. Even with precise stoichiometry, the complete removal of precipitated AgCl by Celite® filtration may compromise catalyst activity.[8] When the activity of various
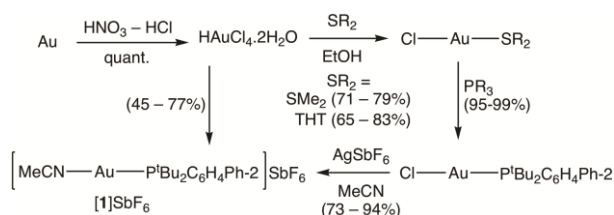
Scheme 3. Multi-step synthesis of Echavarren's Catalyst with reported yields.

catalytic species may vary by orders of magnitude, reliable knowledge of the precise speciation may be critical to understanding, reproducing or refining protocols. In the case of silver-activated gold(I) catalysis, this question, the so-called 'silver effect' has attracted considerable scrutiny,[8,9] including situations where the presence of silver ions or halide may be detrimental or indeed beneficial. Echavarren has shown that the labile salt [Au{NCC$_6$H$_2$(OMe)$_3$-2,4,6}$_2$]SbF$_6$ may serve as a labile precursor for the synthesis of various cationic gold(I) catalysts, however this is also obtained via silver salts, i.e., the reaction of AuCl, AgSbF$_6$ and excess trimethoxybenzonitrile.[10]

Here we report an expedient synthesis of Echavarren's catalyst as the tetrafluoroborate salt [1]BF$_4$ from gold powder, which provides a significant reduction in cost compared to purchasing the catalyst directly, and avoids the need for the tedious procedure including distillation of aqua regia in the synthesis of HAuCl$_4$. Convenience aside, the protocol ensures that the catalyst is *entirely free from halides and silver salts.*

Results and Discussion

Recently we became interested in the development of synthetic protocols for the generation of both Au(I) and Au(III) coordination complexes directly from gold powder. The oxidation of gold powder with the nitrosonium cation ([NO]$^+$) in CH$_3$CN has been shown to give direct access to bis(nitrile) salts of Au(I) including the cation [4]$^+$, however the use of such complexes for further synthetic application remains sparse (Scheme 4).[11] The first report of salts of the [4]$^+$ cation appeared in 1964, however, the instability of the isolated compound as a perchlorate salt precluded structural characterisation.[11j] Work by Wilner and co-workers presented the first crystallographic support for a bis(nitrile) Au(I) complex [4]SbF$_6$, which

was achieved via the treatment of $[Au(CO)_2]SbF_6$ with acetonitrile in super acids.[11k] Krossing and co-workers recently demonstrated the utility of the nitrosonium cation in accessing a host of isolable homoleptic Au(I) acetonitrile salts which differed in the weakly coordinating anion.[12]

Initial investigations conducted by our lab into the utility of $[NO][BF_4]$ as a convenient reagent for accessing gold salts directly from gold powder led to the isolation of the previously inaccessible bis(pyridine) Au(I) tetrafluoroborate salt $[Au(py)_2]BF_4$ [5]BF_4 and the homoleptic tetrakis(pyridine) Au(III) trication $[Au(py)_4](BF_4)_3$ [6]$(BF_4)_3$ (Scheme 4).[13] Wildgoose has also reported the use of the nitrosonium cation for accessing Au(III) in the generation of pincer complexes from Au(I) precursors.[14] We identified [4]BF_4 as a readily accessible Au(I) precursor for the generation of synthetically valuable Au(I) complexes and a potential halide-free replacement for the commonly used Au(I) starting materials $[AuCl(SR_2)]$. In particular, the stoichiometric oxidation of gold powder using $[NO][BF_4]$ avoids the cumbersome distillation of *aqua regia* necessary in accessing chloroauric acid from gold powder (Scheme 3).
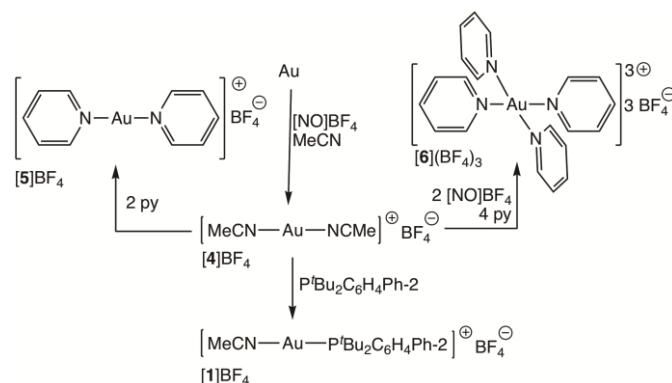
Scheme 4. Homoleptic pyridine complexes[13] and one-pot synthesis of [4]BF_4.

A solution of [4]BF_4 in acetonitrile was freshly prepared from gold powder, using a deficiency (90 mol %) of $[NO][BF_4]$. This solution was vented or sparged with nitrogen to ensure removal of the nitric oxide produced during the oxidation. These precautions are necessary because both NO and $[NO][BF_4]$ react with basic phosphines.[15] The addition of 0.9 equivalents based on gold powder of $P^tBu_2(C_6H_4Ph-2)$ ("Johnphos") to the solution followed by 6 hours stirring resulted in complete disappearance of the peak at $\delta_P = 18.16$ in the $^{31}P\{^1H\}$ NMR spectrum due to free Johnphos and formation of [1][BF_4] ($\delta_P = 57.19$). The desired product is then readily isolated by reducing the solvent volume *in vacuo* and followed by the addition of Et_2O to give a white solid. The solid was then filtered, washed with Et_2O and dried *in vacuo* giving [1][BF_4] in 58% isolated yield based on gold powder or 65% based on $[NO][BF_4]$. Based on NMR monitoring the *in situ* conversion is over 90%. A small impurity (5-10% by ^1H NMR integration) is also observed in both the ^1H and ^{31}P NMR spectra that was identified as the bis Johnphos complex of $[Au]^+$.[16] However, for this impurity to become catalytically active one Johnphos must dissociate, which simply gives the active Eschavarren's catalyst.

Experimental Section

All manipulations were carried out under an atmosphere of dry nitrogen using standard Schlenk line or dry-box techniques. Acetonitrile was dried by distillation under nitrogen from calcium hydride. Gold powder (1.3-2.5 mm) was obtained from Precious Metals Online and $[NO][BF_4]$ was obtained from Sigma-Aldrich. ^1H and $^{31}P\{^1H\}$ NMR spectra were obtained using a 400 MHz Bruker spectrometer. Best results were obtained by protecting the reaction vessel from direct light with aluminium foil.

Synthesis of $[Au(NCMe)(P^tBu_2C_6H_4Ph-2)]BF_4$ [1]BF_4. To a slurry of gold powder (100 mg, 0.51 mmol) in acetonitrile (10 mL) was added $[NO][BF_4]$ (54 mg, 0.46 mmol) and the resulting mixture was stirred in the absence of light for 3 hrs giving a colourless supernatant and traces of residual gold powder. The reaction mixture should be vented under a N_2 atmosphere to allow for the evolution of gaseous NO. The stoichiometry of $[NO][BF_4]$ was kept slightly below 1 equivalent to reduce the possibility of residual oxidant causing ligand oxidation upon addition of the phosphine, which was observed even at this stoichiometry if the addition of the phosphine was within the 3 hr window required for complete oxidation of the gold powder. Residual metallic gold was then removed *via* centrifugation before the addition of $P^tBu_2C_6H_4Ph-2$ ('Johnphos' 137 mg, 0.46 mmol). The reaction was shielded from light and

stirred for a further 6 hrs. The solvent volume was reduced *in vacuo* and the addition of Et_2O yielded a fine white powder which was isolated by filtration, washed with diethyl ether and dried in vacuo. Yield 167 mg (0.27 mmol, 58%).

Conclusion

We have presented a new route to Echavarren's Au(I) catalyst *via* a synthetic approach which avoids the commonly employed *aqua regia* distillation required in accessing many Au(I) scaffolds. While not quite "one-pot" the synthesis is straightforward and requires minimal effort in workup. A cost comparison based on currently available pricings (Precious Metals Online for Au powder, Sigma-Aldrich for all other reagents based on a search on Oct 31st 2017) revealed an approximate 4-fold price decrease per mole between our method and a commercially bought sample of Echavarren's Au(I) catalyst (\$75 mmol^{-1} vs \$350 AUD mmol^{-1}, respectively). An extension of the cost analysis showed that the $[NO][BF_4]$ protocol presented here does not offer a direct reduction in cost compared to the more traditional synthetic method starting with Au powder and *aqua regia* (Scheme 3) however, the costings are comparable at \$46 mmol^{-1} vs \$75 mmol^{-1} making the avoidance of a tedious *aqua regia* distillation (with attendant safety issues) and time savings from the other steps appear favourable. In the context of combinatorial chemistry and high throughput screening of catalyst libraries, the advantage of adding potentially variable phosphine at the final stage, rather than isolating a range of $[AuCl(PR_3)]$ precursors is also a desirable feature.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

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A simple synthesis of Echavarren's Catalyst via oxidation of gold powder with [NO][BF$_4$] in acetonitrile followed by addition of Johnphos is presented.

Just add NOBF$_4$

No silver
No halides