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Synthesis of 2-substituted benzo[*b*]thiophenes via gold(I)–NHC-catalyzed cyclization of 2-alkynyl thioanisoles

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Benzo[*b*]thiophene heterocycle is an important component of many important small molecule pharmaceuticals and drug candidates as well as organic semiconducting materials. Many methods have been developed for construction of benzo[*b*]thiophene core via cyclization reaction of alkynes. Although few catalytic reactions were disclosed, most methods rely on stoichiometric activation of alkyne. Here we report an efficient method for synthesis of 2-substituted benzo[*b*]thiophenes from 2-alkynyl thioanisoles catalyzed by gold(I)–IPr hydroxide that is applicable to a wide range of substrates with diverse electronic and steric properties. Additionally, we demonstrate experimentally that the acid additive and its conjugate base are essential to catalyst turnover.

Introduction

Benzo[*b*]thiophene is an established heterocyclic scaffold for preparing organic small molecules that display an array of important properties (Figure 1). For example, materials based on BTBT, [1]benzothieno-[3,2-b]benzo-thiophene (**1**), are superior organic semiconductors used in air-stable high-performance organic field-effect transistors (OFETs).[1] Zileuton (**2**) and sertaconazole (**3**) are benzo[*b*]thiophene-containing pharmaceuticals currently on the market for treatment of asthma and fungal infections, respectively.[2] Also, new drug candidates such as **4**[3] and others[4] are being actively developed, and for some compounds, presence of sulfur can be the determining factor in biological activity. For example, the binding affinity of analogs of benzo[*b*]thiophene-2-ylboronic acid that lack the electron-rich sulfur heterocycle can be up to three orders of magnitude lower.[4d] Therefore, efficient and selective methods for construction of substituted benzo[*b*]thiophenes have been a focus of considerable research efforts.

Multiple approaches have been developed for the synthesis of benzo[*b*]thiophenes (Scheme 1). For example, cyclization of 2-alkynyl aryl thiols and sulfides where the unsaturated carbon is activated with strong electrophile (route **I**) is a well-documented pathway to 2,3-disubstituted benzo[*b*]thiophenes.[5] Benzo[*b*]thiophene heterocycle can also be formed in a reaction of lithiated *o*-alkynylbenzenes with sulfur and subsequent cyclization of the generated thiolate anion (route **II**).[6] Palladium complexes were shown to catalyze cross-coupling reactions with subsequent formation of thiophene ring (route **III**).[7] Although a broad range of substituted benzo[*b*]thiophenes can be accessed rapidly, the reactions require high catalyst loading (typically 5–10%) and harsh reaction conditions. 2-Alkynyl aryl sulfides readily cyclize in the presence of palladium or gold catalysts (route **IV**)[7c, 8] but these methods are limited to substrates containing specific substituents on sulfur and relatively high catalyst loading is typically required. Several radical-mediated syntheses of benzothiophenes, including light-mediated reactions,[9] as well as direct functionalization of benzo[*b*]thiophenes[10] have also been published.

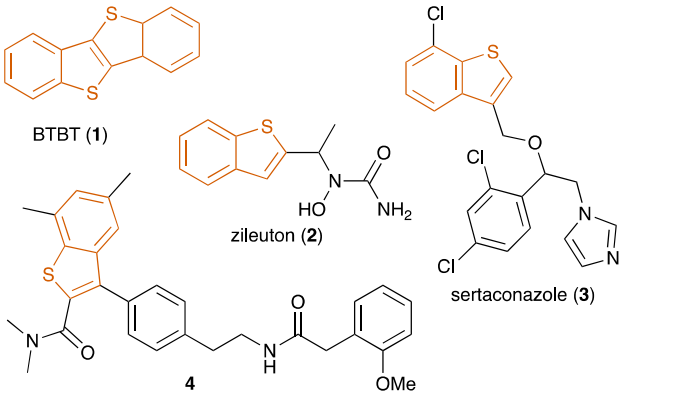

Figure 1. Examples of materials and pharmaceuticals containing benzo[*b*]thiophene heterocycle

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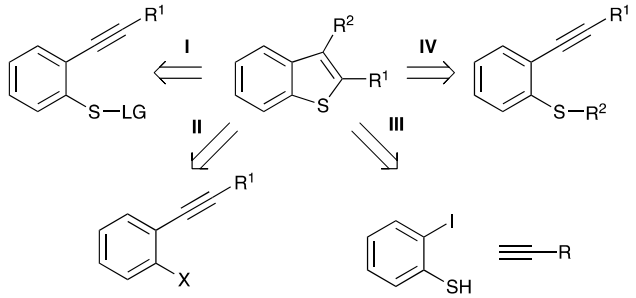
† Electronic Supplementary Information (ESI) available: synthetic procedures, results of reaction optimization studies, spectroscopic data for synthesized compounds, and digital images of NMR spectra. See DOI: 10.1039/x0xx00000x



Scheme 1 Overview of selected methods for synthesis of benzo[*b*]thiophene core

Over the last two decades, homogeneous gold(I) catalysis has emerged as a vibrant area of research.[11] Catalysts based on gold(I) are tolerant towards moisture and air (high oxidation potential), offer high catalyst turnovers,[12] and are less toxic than other pi-acidic transition metals. Cationic gold(I) complexes are now standard catalytic systems for activation of alkynes towards nucleophilic additions of a range of heteroatom-containing nucleophiles.[13] In recent years, the use of *N*-heterocyclic carbenes (NHCs)[14] as ligands for cationic gold(I) complexes rapidly gained interest led by contributions of Nolan and co-workers.[15] The main features of NHCs is strong p-donating ability combined with highly tuneable sterics, which is preferable whenever highly active but stable metal center is desired. *N*,*N*'-(2,6-diisopropylphenyl)dihydroimidazolium (**IPr**), shown in Figure 2, has been established as a nearly universal ligand for gold(I) complexes used in alkyne addition reactions.[16] Nakamura and co-workers demonstrated that *o*-alkynylphenyl sulfides containing very electron rich substituents on sulfur such as *O*,*S*-acetals, trialkylsilyl, and *p*-anisyl will undergo AuCl-catalyzed cyclization with concurrent migration of the substituent from sulfur to C–3.[8] However, to the best of our knowledge, there is no successful example of gold(I)-catalyzed cyclization of more widely available thioanisoles. Here we report an efficient method for gold(I)–NHC-catalyzed synthesis of benzo[*b*]thiophenes from 2-alkynyl thioanisoles. For our model substrate, the reaction proceeds efficiently in presence of only 0.5 mol % of Au(IPr)Cl or Au(IPr)OH. Notably, the reaction only occurs in presence of a Brønsted acid of sufficient strength.

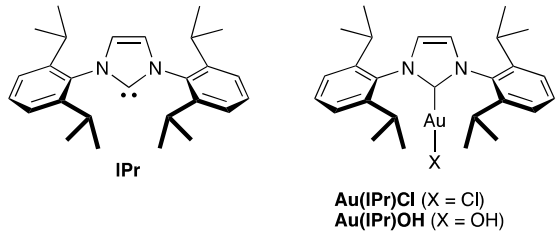
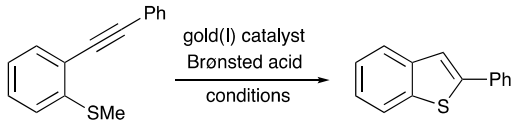


Figure 2. Gold(I)-NHC complexes evaluated in this study.

Results and discussion

Our studies initiated with the reaction of 2-(phenylethynyl)thioanisole (**5a**) in presesnce of 5 mol% of common gold(I) complexes in toluene at 80°C (Table 1, entries 1–4), but these preliminary experiments returned unreacted starting material. Upon inspection of ^{1}H NMR of the crude reaction

Table 1. Optimization of reaction conditions



5a **6a**

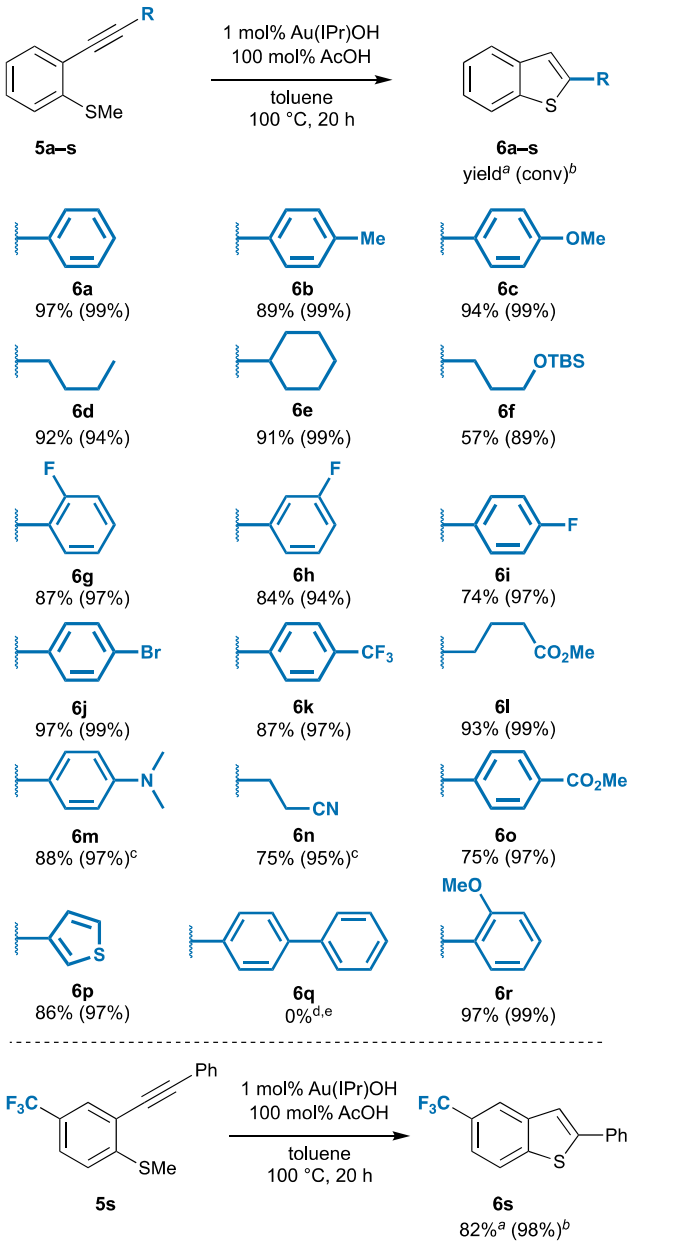
Entry	Catalyst [mol%]	Additive	Conditions	Conversion [%][a]	Yield [%]
1	AuCl [5]	–	toluene, 80 °C, 20 h	<5	
2	Au(PPh$_3$)Cl [5]	–	toluene, 80 °C, 20 h	<5	–
3	Au(PPh$_3$)BF$_4$ [5]	–	toluene, 80 °C, 20 h	<5	–
4	Au(IPr)OH [5]	–	toluene, 80 °C, 20 h	<5	–
5	Au(IPr)OH [20]	–	toluene, 80 °C, 20 h	15	–
6	Au(IPr)OH [5]	H_2O	toluene, 80 °C, 20 h	<5	–
7	Au(IPr)OH [5]	MeOH	toluene, 80 °C, 20 h	<5	–
8	Au(IPr)OH [5]	AcOH	toluene, 80 °C, 20 h	99	95
9	Au(IPr)OH [5]	Et_3N	toluene, 80 °C, 20 h	–	–
10	Au(PPh$_3$)BF$_4$ [5]	AcOH	toluene, 80 °C, 20 h	<5	–
11	Au(IPr)OH [0.5]	AcOH	toluene, 80 °C, 6 h	92	–
12	Au(IPr)Cl [0.5]	AcOH	toluene, 80 °C, 6 h	75	–
13	Au(IPr)Cl [0.5]	AcOH	MeCN, 80 °C, 6 h	22	–
14	Au(IPr)Cl [0.5]	AcOH	AcOH, 80 °C, 6 h	71	–
15	Au(IPr)Cl [0.5]	AcOH	no solvent, 80 °C, 6 h	91	–
16	Au(IPr)Cl [0.5]	AcOH	toluene, 100 °C, 20 h	99	92[c]
17	Au(IPr)OH [0.5]	AcOH	toluene, 100 °C, 20 h	99	97[c]
18	Au(IPr)Cl [1]	AcOH	toluene, 100 °C, 1 h	3	–
19	Au(IPr)OH [1]	AcOH	toluene, 100 °C, 1 h	58	–
20	Au(IPr)OH [1]	AcOH	toluene, 100 °C, 20 h	99	97[c]

[a]Conversion was determined using ^{1}H NMR analysis (100% method) of post-reaction mixtures. [b]Isolated yield after chromatography. [c]Average of three experiments

mixture in which Au(IPr)OH was used as catalyst (Table 1, entry 4). we noticed formation of a new species that was not present in reactions catalyzed by AuCl or gold(I)–phosphine complexes (entries 1–3). The relative amount of the new product increased when 20 mol% of Au(IPr)OH was used (Table 1, entry 5), but the resonances for the new compound did not match the chemical shifts for the expected product, 2-phenylbenzo[*b*]thiophene (**6a**). We didn't observe shifts of the SCH_3 group in ^{1}H NMR spectrum suggesting that binding of sulfur to gold(I) center is not pronounced. However, chemical shifts of resonances corresponding to isopropyl groups of the IPr ligand were shifted compared to the NMR of the pure gold(I) hydroxide complex.[17] We hypothesized that the new species might be the vinyl gold intermediate **7** (see discussion of the mechanism below), but attempts of isolating **7** were unsuccessful. It is worth noting that Nakamura and co-workers observed productive gold(I)-catalyzed cyclization only when sulfur was substituted with highly electron-rich groups that can stabilize the positive charge that develops on carbon during migration. Migration of the silyl or *p*-anisyl group from sulfur to the vinyl carbon bound to gold releases the metal and allows for catalyst turnover.[8] Since the methyl group is insufficiently stabilized to migrate to the vinyl position, we considered adding Brønsted acid to facilitate recycling of the catalyst through protodeauration. Water and methanol (Table 1, entry 6 and 7, respectively) were not

effective protodeauration additives. To our delight, when 1 equiv. of acetic acid was added, complete conversion of the starting material was observed and benzo[*b*]thiophene product was isolated in 95% yield (entry 8). Conversely, reaction of **5a** in presence of 1 equiv. of triethylamine returned unreacted substrate (entry 9). Catalytic activity appears to be specific to gold(I)–NHC complexes because gold(I)–phosphine catalysts with non-coordinating counterions such as Au(PPh_3)BF, did not yield **6a** when acetic acid was added (entry 10). We then investigated the catalyst turnover limits and found that the reaction is nearly complete (92% conversion) after 6 h with only 0.5 mol% of Au(IPr)OH (entry 11). We also found that less expensive, more widely available Au(IPr)Cl can catalyze the cyclization, but the reaction is slower (entry 12). We used the slower reaction catalyzed by Au(IPr)Cl to probe the effect of solvent on the reaction. The reaction is significantly slower in polar nonprotic solvent such as acetonitrile (entry 13). Protic solvents such as ethanol and acetic acid (entry 14) are also applicable, but longer reaction time is required and catalyst decomposition was often observed. We observed significant conversion (91%) in reaction carried out without solvent (entry 15), but solvent-free conditions did not translate universally to other substrates and we recommend using small amount of non-polar solvent such as toluene. Additionally, intermolecular addition reaction between the alkyne and ethanol or acetic acid is significantly slower because we did not observe the typical products of hydroalkoxylation or hydroacetoxylation.[13d] Gold(I)–IPr chloride catalyst is capable of fully converting the alkyne to benzo[*b*]thiophene because after 20 h yields obtained with the chloride and hydroxide catalyst are comparable (entries 16 and 17). There appears to be, however, an induction period for the chloride catalyst. After 1 h the reaction catalyzed by Au(IPr)Cl shows that only 3% of alkyne reacted (entry 18) compared to 58% for Au(IPr)OH (entry 19). We think it's partially due to insolubility of Au(IPr)Cl in the reaction mixture for the first 2 hours of heating. Preliminary survey of other substrates indicated that some derivatives react slower than alkyne **5a**. Thus, for the study of substrate scope and we modified the general reaction conditions to use 1 mol % of Au(IPr)OH in toluene at 100 °C for 20 h.

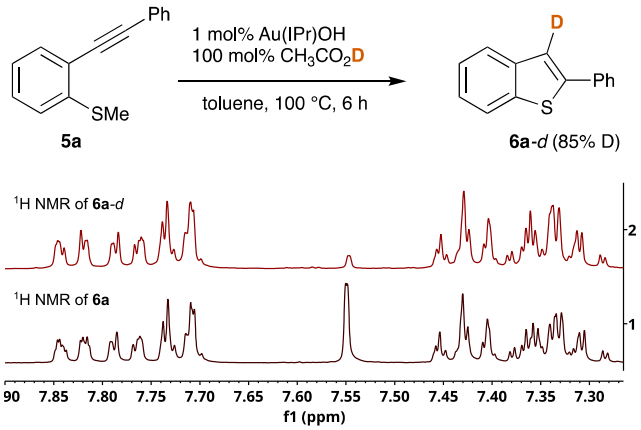
With optimized reaction conditions in hand we began exploring the substrate scope of substituted 2-ethynyl thioanisoles for the gold(I)-catalyzed cyclization (Scheme 2). A variety of different substitutions were well tolerated under the reaction conditions.‡ In general, substrates containing electron-rich and alkyl substituents delivered corresponding benzo[*b*]thiophenes in excellent yields. The position of electron-withdrawing substituent on the aromatic substituent (**5g**–**5i**) has little effect on the product yield. Alkyne substituted with (4-trifluoromethyl)phenyl group readily converts to benzothiophene as evidenced by level of substrate consumption. However, limited solubility of the product hampers chromatographic purification. When we carried out the reaction on a larger scale, the isolated yield improved because the product could be purified by trituration with cold methylene chloride. Alkynes containing Lewis-basic functional groups such as dimethylamino (**5m**) and ester (**5o**) reacted slower in comparison and it was necessary to double the amount of catalyst to achieve complete consumption of the starting material. Reaction of bisphenyl-substituted alkyne **5q** was unsuccessful, even with 5 mol% of the catalyst, which we attribute to very low solubility of **5q** in toluene. When the reaction was carried out in toluene–THF (1:1 v/v), we observed consumption of the alkyne but the reaction mixture contained multiple products and isolation of **6q** was unsuccessful. The reaction is also applicable to substrates carrying substitutions on the parent thioanisole ring. Reaction of trifluoromethyl derivative **5s** was efficiently converted to the corresponding benzo[*b*]thiophene (NMR yield >97%). Low solubility of **6s** allowed for isolation by direct filtration from the reaction mixture.



Scheme 2. The substrate scope of gold(I)-catalyzed synthesis of benzo[*b*]thiophenes from 2-alkynyl thioanisoles. [a]Isolated yield. [b]Conversion was determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c]2 mol% of catalyst was used. [d]5 mol% of catalyst in toluene–THF (1:1, v/v). [e]The reaction returned a complex mixture of products and isolation of the expected benzo[*b*]thiophene was unsuccesful.

Reaction mechanism

We then performed control experiments to gain more insight into the mechanism. When the reaction of alkyne **5a** was carried out in presence of 1 equiv of acetic acid-*d*, ^{1}H NMR showed approximately 85% of deuterium incorporation at the vinylic position (Scheme 3), which confirms involvement of acetic acid in protodeauration and catalyst turnover.



Scheme 3. Reaction carried out in the presence of acetic acid-*d* produces benzo[b]thiophene with up to 85% isotopic enrichment at the vinylic position as shown by reduced intensity of vinylic resonance.

It was unclear, however, what is the fate of the sulfide methyl group. We hypothesized that the methyl group is transferred from the methylsulfonium anion to the acetate anion generated during protodeauration to give methyl acetate. ^{1}H NMR analysis of unpurified post-reaction mixture without removing the solvent shows two additional singlet resonances of equal integration at 2.06 and 3.67 ppm (see ESI for details). The chemical shifts matched the expected values for methyl acetate and suggested involvement of the acetate anion in the catalytic cycle. This hypothesis was tested by carrying out the reaction using ethyl sulfide derivative **5t**. Proton spectrum of post-reaction mixture (Figure 3, bottom) showed complete consumption of **5t** (Figure 3, top) indicated by disappearance of quartet at 3.2 ppm and presence of resonance at 4.2 ppm characteristic of methylene group in ethyl acetate, and thus confirming transfer of the alkyl group from sulfide to acetate. The ratio of ethyl acetate to product was approximately 1:1 suggesting it is the main alkyl transfer pathway under the reaction conditions.

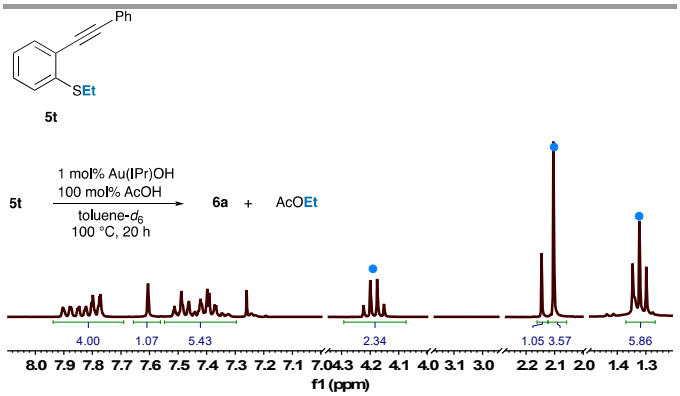
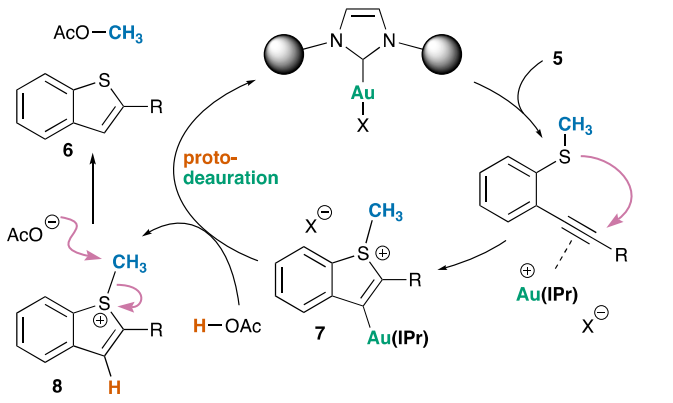


Figure 3. Proton NMR spectra ($CDCl_3$) of alkyne **5t** (top) and post-reaction mixture (bottom) showing resonances for the ethyl group transferred from sulfide (1.4 and 3.2 ppm) to acetate (1.3 and 4.2 ppm) unreacted acetic acid (2.1 ppm).

Our experimental observations are consistent with the mechanism presented in Scheme 4 and reveal that carboxylic acid and its conjugate base both play a role in the overall transformation. Research by Nolan and co-workers[18] suggests that under the reaction conditions the hydroxide anionin Au(IPr)OH will rapidly exchange with acetic acid and the acetate is likely the counterion in the active catalyst (X = OAc in Scheme 4). The metal center coordinates to alkyne pi electrons and activates the carbon toward nucleophilic attack by sulfur of the methyl sulfide to give vinyl gold intermediate **7**. Acetic acid facilitates collapse of the vinyl gold complex through protodeauration to produce methylsulfonium intermediate **8** and acetate anion.[19,20] The methyl group is then transfered from sulfur to oxygen of the acetate to give the product and methyl acetate.



Scheme 4. Plausible mechanism of gold(I)-NHC-catalyzed cyclization of 2-alkynyl thioanisoles.

Conclusions

We developed an efficient method for synthesis of 2-substituted benzo[*b*]thiophenes. The reaction is catalyzed by gold(I)-IPr hydroxide complex and proceeds smoothly with as little as 0.5 mol% of the catalyst. The reaction tolerates a broad range of substrates and can be carried out in air using commercial grade reagents and solvents. Additionally, we demonstrated experimentally that a Brønsted acid and its conjugate base are necessary for catalyst turnover.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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Notes and references

‡ Preparation of 2-phenylbenzo[*b*]thiophene (**5a**): In a 2-dram vial was added the catalyst (2.50 mmol), alkyne (0.250 mmol) acetic acid (15.0 µL, 0.250 mmol) and toluene (240 µL). The vial was capped and the mixture heated at 100 °C for 20 h. The mixture was then cooled to rt and the product was purified by flash column chromatography (SiO_2, 2% ethyl acetate in hexanes) to give product as white solid (51.0 mg, 97%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (ddd, *J* = 7.2, 1.9, 0.8 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.79 – 7.72 (m, 2H), 7.59 (d, *J* = 0.8 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.43 – 7.32 (m, 3H).

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20 During peer review of this manuscript it was suggested by one of referees that the sulfide group might bind to gold(I) center deactivating it and the role of Brønsted acid is to disrupt binding by reversible protonation of the sulfide. When a solution of alkyne and catalyst was examined by ^1H NMR we observed chemical shift changes for the IPr ligand but we did not observe changes in chemical shift of

the alkyl sulfide group. Thus, we believe the role of Brønsted acid additive is limited to protodemetallation process.