

1,2,3-Triazole as a Special “X-Factor” in Promoting Hashmi Phenol Synthesis

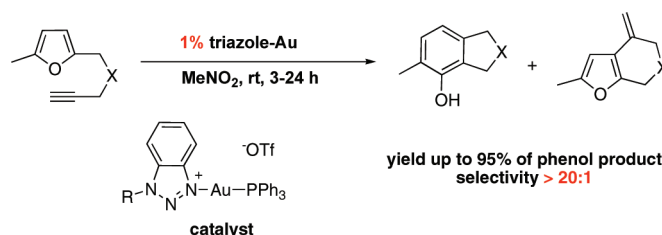
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Received November 20, 2009

ABSTRACT



³¹P NMR experiments revealed rapid decomposition of the Ph₃PAu⁺TfO[−] complex in the presence of the furan-yne, which resulted in poor reactivity as reported in the literature. Therefore, instead of tuning different ligands (PR₃), the 1,2,3-triazole was applied as a special X-factor to stabilize the catalyst. The desired phenol products were prepared in excellent yields (1% cat. up to 95% yield) and chemoselectivity (>20:1).

In the past several years, homogeneous Au catalysis has become one very important research area in organic synthesis.¹ With the discoveries of more and more interesting new transformations, attention has been drawn to the understanding of the reaction mechanism and the actual catalytic component.² We recently reported 1,2,3-triazole bound Au complexes as effective, thermally stable catalysts in intermolecular alkyne hydroaminations.³ Herein, we report the application of these complexes as effective precatalysts in promoting chemoselective intramolecular furan-alkyne cy-

clization, which provided (a) clear evidence for the Au(I) cation as a possible catalyst in this transformation and (b) a practical alternative solution that allows simple, inexpensive PPh₃ as an effective ligand.

As well-documented in the literature, the cationic Au activation of alkynes usually proceeded through two competitive reaction paths: (a) Lewis acid (or π -acid) activation of alkyne for nucleophilic addition and (b) Au back bonding to alkyne that led to the formation of carbene-like intermediates. One good example for this interesting dual reactivity is the Au-catalyzed intramolecular alkyne-furan arrangement, first reported by Hashmi and co-workers.⁴

The furan-yne **1** could rearrange to form aromatic substitution product **A** and phenol **B** with the presence of proper Au catalysts (Scheme 1), although with some debate it was generally believed that product **A** was formed through arene addition to the gold (Lewis acid) activated alkyne (Friedel–Craft-type addition). The formation of phenol **B**, on the other hand, proceeded through the Au–carbene like intermediates followed by cyclopropane ring opening and gold carbene cyclization. Compared with reaction path A, the formation of phenol **B** is

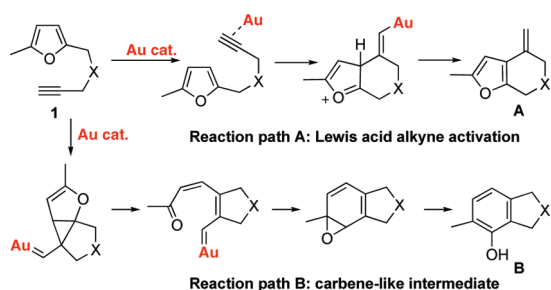
(1) For selected recent reviews on homogeneous Au catalysis, see: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (h) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (i) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936.

(2) Selected recent examples, see: (a) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225–1228. (b) Gorske, B. C.; Mbofana, C. T.; Miller, S. J. *Org. Lett.* **2009**, *11*, 4318–4321. (c) Marion, N.; Carlqvist, P.; Gealageas, R.; de Fremont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437–6451. (d) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155–3164.

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Scheme 1. Dual Reactivities of Cationic Au Catalysts



a much more interesting transformation, which involved four bonds breaking and formation of four new bonds in one step. Hashmi and co-workers performed extensive investigations of this transformation (Figure 1).⁵ Remarkable works have also

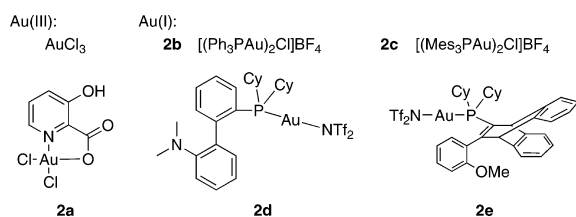


Figure 1. Representative effective gold catalysts for Hashmi phenol synthesis.

been performed regarding the elucidation of the reaction mechanism including the successful isolation of several key intermediates.⁶ Our interest in spending efforts on this rather “well-studied” transformation was initiated by the “unconventional” and “picky” ligand effects (vide infra), along with an unclear argument in the literature whether the Au(I) cation itself could promote this reaction or the in situ formed Au(III) (from Au(I) precatalyst decomposition) were the only viable catalysts for this reaction.

According to the literature, AuCl₃ was first reported as the effective catalyst for the isomerization of **1**, giving phenol **B** as the major products in good yields.⁴ Later developed Au(III)–pyridine complexes (such as **2a**) led to improved reaction efficiency.⁷ Meanwhile, the Au(I) complexes, such as Ph₃PAuOTf, were reported as less effective catalysts with “slow reaction rate” and poor

chemoselectivity. One hypothesis was that Au(I) underwent disproportionation and generated active Au(III) in situ, which then served as the active catalyst for this reaction.^{5i,8} The successful application of Au(I) complexes as the precatalyst was first reported in 2006, while Uson–Laguna salt **2b** and Schmidbaur–Bayler salt **2c** were used to promote the reaction, giving modest to good yields (up to 72%) of the phenol products.⁸ Interestingly, with a more sterically hindered ligand, catalyst **2c** provided better chemoselectivity, favoring the formation of the phenol (>20:1). Therefore, very recently, new Au(I) complexes with steric hindered ligands (such as **2d** and **2e**) have been applied as effective catalysts for phenol synthesis. These results led to the concerns: *Were Au(I) cations themselves effective catalysts for alkyne 1 activation? Was the application of the rather complicated steric hindered and electron enriched phosphorus ligands necessary?*

It was reasonable to rationalize that Au(III), a better Lewis acid, should favor alkyne activation in the Friedel–Craft type cyclization (formation of **A**). The Au(I) cation, in theory, would be a better catalyst for carbene intermediate formation due to its high electron density on the gold atom (d¹⁰ for Au^I and d⁸ for Au^{III}), but this hypothesis was not consistent with current literature reports. To investigate the reaction mechanism, ³¹P NMR studies were performed with substrate **1a** and simple Ph₃PAu⁺·TfO[−] catalyst as summarized in Figure 2.

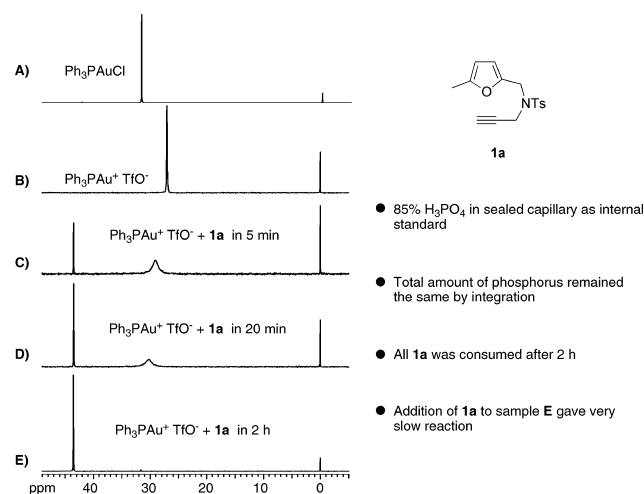


Figure 2. ³¹P NMR spectra of catalyst Ph₃PAu⁺·TfO[−] with substrate **1a**. Ph₃PAuCl (20 mg, 0.04 mmol) was dissolved in 1 mL of CDCl₃, then AgOTf (10 mg, 0.04 mmol) and **1a** (24 mg, 0.08 mmol) were added sequentially (see Supporting Information).

To ensure the accuracy of these NMR experiments, the H₃PO₄ in a sealed capillary tube was applied as the internal standard (0 ppm signal). The Ph₃PAu⁺·TfO[−] sample was freshly prepared. As shown in Figure 2B, the Ph₃PAu⁺, though it decomposed over time (up to 10 h at rt), could be prepared in good purity. The integration ratio of the signals provided direct measurement of PPh₃Au⁺ cation concentration. Upon the addition of 2.0 equiv of alkyne **1a**, formation of gold-mirror occurred *instantly*. A new 43.5 ppm signal was observed in

(5) See examples: (a) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzic, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 5848–5852. (b) Hashmi, A. S. K.; Loos, A.; Littmann, A.; Braun, I.; Knight, J.; Doherty, S.; Rominger, F. *Adv. Synth. Catal.* **2009**, *351*, 576–582. (c) Hashmi, A. S. K.; Schäfer, S.; Bats, J. M.; Frey, W.; Rominger, F. *Eur. J. Org. Chem.* **2008**, *73*, 4891–4899. (d) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 6991–6996. (e) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709–713. (f) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejovic, E.; Frost, T. M.; Miehlisch, B.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2006**, *12*, 5806–5814. (g) Carretin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2006**, *348*, 1283–1288. (h) Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem.—Eur. J.* **2003**, *9*, 4339–4345. (i) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771.

NMR (Figure 2C), which likely was attributable to the corresponding phosphorus oxidation products. The decomposition of the $\text{Ph}_3\text{PAu}^+\text{TfO}^-$ occurred much faster with the presence of alkyne **1a** and almost no Ph_3PAu^+ left after 2 h (Figure 2E). Importantly, **1a** was completely consumed, and the products **3a** (26% NMR yield) and **4a** (28% NMR yield) were both formed, though with low yields and poor chemoselectivity. Upon addition of extra **1a** into the fully decomposed sample (Figure 2E), a slower reaction of **1a** was observed, which was consistent with literature reports that in situ formed Au(III) or Au(0) from Au(I) decomposition could still catalyze this transformation, though with a slower reaction rate. These NMR experiments indicated that (a) the reaction between $\text{Ph}_3\text{PAu}^+\text{TfO}^-$ and **1a** was fast and (b) the resulting low yields were caused by the decomposition of the Au(I) catalyst, especially with the presence of **1a**. These results were also in agreement with the facts that more bulky phosphorus ligands (i.e., **2d**, **2e**) gave better yields due to the improved stability of Au(I) cations.

Recently, we reported the application of triazole–Au complexes as thermally stable catalysts in challenging alkyne activation under harsh conditions.³ The working hypothesis was that triazole compounds could form dynamic coordination with Ph_3PAu^+ cation, which allowed the effective activation of alkyne with much improved gold cation stability. This discovery was very interesting since it provided an alternative strategy in tuning the Au catalyst reactivity (Figure 3): *instead of changing different phosphorus ligands,*

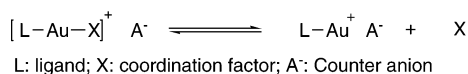


Figure 3. X-factor: an alternative strategy in tuning gold catalyst reactivity.

the catalyst reactivity could be adjusted by the X ligands through controlling the equilibrium process.

Considering the main problem for simple $\text{Ph}_3\text{PAu}^+\text{TfO}^-$ in promoting Hashmi phenol synthesis was the decomposition of catalysts, we wondered whether the X-ligand coordination strategy could be applied. This would provide an alternative solution to promote this useful transformation with the very simple, inexpensive PPh_3 ligand. The NMR experiments between triazole–Au complex **2g** and **1a** were then performed to evaluate the stability of the triazole–Au complex (Figure 4).

To our great delight, no triazole Au decomposition was observed with the presence of **1a** even after 24 h, and

(6) (a) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfe, M.; Frey, W.; Bats, J. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2798–2801. (b) Hashmi, A. S. K.; Kurpejovic, E.; Wölfe, M.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2007**, *349*, 1743–1750. (c) Hashmi, A. S. K.; Rudolph, M.; Siehl, H.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem.—Eur. J.* **2008**, *14*, 3703–3708.

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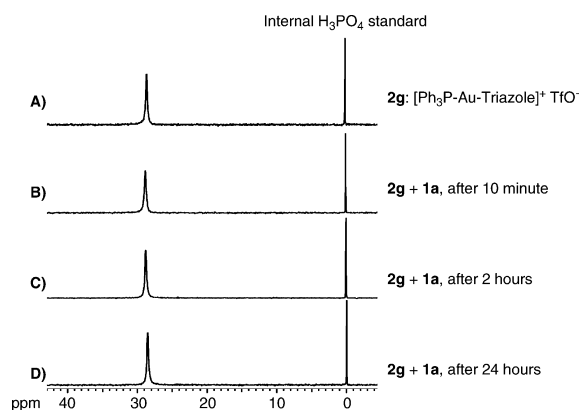


Figure 4. ^{31}P NMR Spectra of Complex **2g** with Substrate **1a**. **2g** (30 mg, 0.04 mmol) was dissolved in 1 mL of CDCl_3 , and then **1a** (24 mg, 0.08 mmol) was added (see Supporting Information).

isomerization products **3a** and **4a** were formed in modest yields (Table 1, entry 1). Detailed screening of the reaction conditions is shown in Table 1.

Table 1. Screening of Reaction Conditions

							yield (%) ^a		
	loading		[C]	time	convn		3a	4a	3a:4a ^b
	cat.	(%)	soln	mol/L	(h)	(%)			
1	2f	2.0	CH_2Cl_2	0.2	4	100	24	28	1:1.2
2	2g	2.0	CH_2Cl_2	0.2	4	100	30	34	1:1.1
3	2f	2.0	DCE	0.2	4	100	35	30	1.2:1
4	2f	2.0	Tol	0.2	4	95	45	trace	>20:1
5	2f	2.0	CH_3CN	0.2	4	100	54	7	8:1
6	2f	2.0	CH_3NO_2	0.2	4	100	56	0	>20:1
7	2g	2.0	CH_3NO_2	0.2	4	100	59	0	>20:1
8	2g	5.0	CH_3NO_2	0.02	8	96	90	0	>20:1
9	2g	1.0	CH_3NO_2	0.05	8	73	68	0	>20:1
10	2g	0.5	CH_3NO_2	0.075	21	65	63	0	>20:1
11	2g	1.0	CH_3NO_2	0.075	12	100	96	0	>20:1

^a Yields determined by NMR with 1,3,5-trimethoxybenzene as internal standard. ^b Ratio determined by NMR of crude reaction mixtures.

As shown in Table 1, with application of triazole, the catalyst **2f** could effectively promote alkyne **1a** rearrangement, giving **3a** and **4a** in modest yields. The chemoselectivity (**3a:4a**) was poor when the reaction was conducted in dichloromethane. However, the selectivity was significantly improved with nitromethane as the solvent, giving phenol **3a** as the dominant product (entry 6). Catalyst **2g** gave slightly improved yield (entry 7), which was likely due to the improved catalyst stability. Notably, the crude reaction NMR indicated that the only side

reaction was the polymerization of **1a**. Therefore, to further improve the reaction performance, dilution was applied (favoring the desired *intramolecular* rearrangement over the competing *intermolecular* polymerization). As expected, excellent yields were received when the reaction was performed at lower concentration even with reduced catalyst loading, though slower reaction rates were associated (entries 8–11). Combining the effect of dilution and decreasing catalyst loading, 1% catalyst with 0.075 M concentration was selected as the practical, optimal condition, with the formation of product in nearly quantitative yield (entry 11).

With this 1,2,3-triazole coordination, *even the simple PPh₃ bound Au(I) cation* could become a highly efficient catalyst for this transformation. To evaluate the generality of this simple precatalyst, some representative furan-alkynes were tested, and the phenol products were obtained in excellent yields as shown in Figure 5.

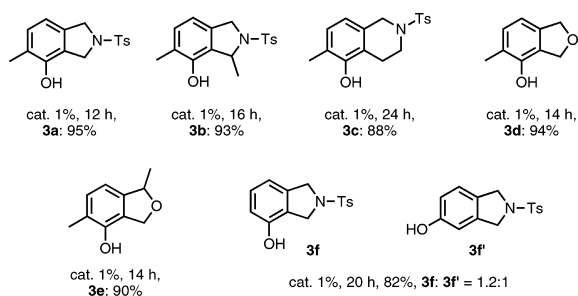


Figure 5. Representative substrates with triazole–Au catalysts. Reaction performed at room temperature and with the concentration 0.075 mol/L in nitromethane. Isolated yields.

As shown in Figure 5, this triazole–Au precatalyst was suitable for all of the tested furan-alkyne substrates, giving the desired phenol products in excellent yields. For the α -unsubstituted alkyne **1f**, two different cyclization products, **3f** and **3f'**, were obtained, which was consistent with the proposed reaction mechanism in the literature.

According to the literature, it was generally believed that Au(I) complexes possessed two coordination sites with a 180° bond angle. However, some recent reports suggested that it was possible to have a “third coordination” of highly electron-rich substrates through static charge interaction.^{2b} One recent example was the chiral anion controlled enantioselective Au(I)-catalyzed intramolecular hydroamination reported by Toste.⁹ Owing to the significantly improved reactivity of the [Ph₃P–Au–triazole]⁺·TfO[–] catalyst, we wondered whether

[Ph₃P–Au–triazole]⁺ was the actual catalyst rather than the Ph₃PAu⁺ cation. The kinetic triazole titration experiments were therefore performed as shown in Figure 6.

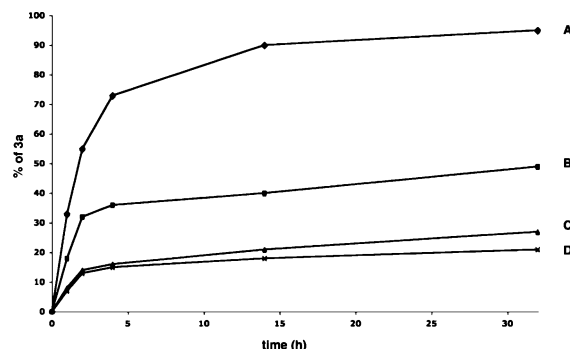


Figure 6. Reaction kinetic profiles with various amounts of triazoles in the system. General reaction conditions: **1a** and catalyst **2g** in CH₃NO₂, concentration was 0.04 mol/L, room temperature. Yields of **3a** were determined by the NMR of the reaction mixture at given time with 1,3,5-trimethoxybenzene as internal standard. **A**: 1% **2g**. **B**: 1% **2g** + 1% triazole. **C**: 1% **2g** + 4% triazole. **D**: 1% **2g** + 9% triazole.

The reaction kinetic profile indicated a significant decrease in reaction rate with increase of triazoles. These experiments provided strong evidence that the actual Au(I) catalyst was likely the Ph₃PAu⁺ cation, which was under equilibrium with [Ph₃P–Au–triazole]⁺.

In conclusion, the NMR experiments revealed that the reason for simple Au(I) catalyst as a poor catalyst in promoting Hashmi phenol synthesis was the rapid decomposition of the gold catalyst. Therefore, instead of tuning the phosphorus ligands, an alternative strategy was developed by using the 1,2,3-triazole as a coordination factor to stabilize the catalyst. Excellent yields and chemoselectivity were obtained. This new approach not only provided a simple solution for the reported transformation but also, more importantly, revealed a new strategy in fine-tuning catalyst reactivity. Influences on the reactivities of other gold-catalyzed transformations by this X-factor effect are expected and currently under investigation.

Acknowledgment. We thank the NSF (CHE-0844602), DOE (DE-FC26-04NT42136), and ACS-PRF-47843-G1 for financial support.

Supporting Information Available: Experimental details and spectrographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL902680K

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