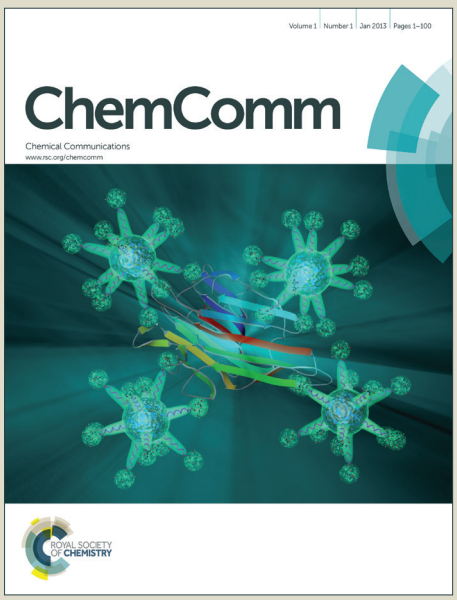
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

Communication

Quantitative Kinetic Investigation of Triazole-Gold(I) Complex Catalyzed [3,3]-Rearrangement of Propargyl Ester

Yumeng Xi,[a] Qiaoyi Wang,[a] Yijin Su,[a] Minyong Li,*[b] and Xiaodong Shi*[a]

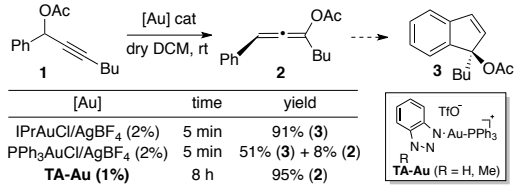
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The triazole-gold(I) complex catalyzed [3,3]-rearrangement of propargyl ester has been quantitatively investigated through *in situ* IR. First order on [Au] and [propargyl ester] suggested that the turnover-limiting step is the associative ligand substitution. The activation enthalpy was also determined to be 7.8 kcal/mol. TA-Au catalysts with different triazole derivatives were also tested, giving a linear free energy relationship with a ρ value of 0.74.

The past decade has witnessed the fast growing homogenous gold catalysis.[1] Compared with the fast paces of new transformation development, the mechanistic investigations left much behind. Meanwhile, with recent efforts in characterizing catalytic intermediates using X-ray crystallography and NMR,[2] more and more evidences suggest that much more complicated mechanism is operative in real case rather than the oversimplified mechanism previously assumed. Furthermore, the recent observation of "silver effect",[3] Au-Cl-Ag[4] and Au-Cl-Au[5] complexes, and "small gold cluster" catalysis[6] further supports the more complex mechanism, and stimulates the need of mechanism study. In general, gold catalysis involves three important steps: coordination (to alkyne/alkene), protodeauration and gold decomposition (side reaction).[7] Thus, due to the mechanistic complexity (especially the existence of fast decomposition), efforts to target each elementary step in catalytic cycle are not always fruitful.[8] Thank to the recent mechanistic works from several laboratories, meaningful data were derived from some stoichiometric reactions,[9] although they may not necessarily reflect the catalytic reactions accurately.

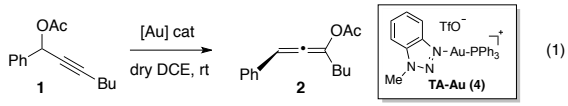
In 2009, our group introduced 1,2,3-triazole bound cationic gold(I) complex (TA-Au) as an improved thermally stable catalyst.[10] Later it was discovered that the TA-Au could preferentially activate alkyne over allene in propargyl ester [3,3]-rearrangement,[11] where indene was synthesized using 2 mol% $IPrAuCl/AgBF_4$.[12] However, in our case, no indene was detected after 12 h using 1 mol% TA-Au. We view this phenomenon as a good opportunity for mechanistic study. The simplified system (over Nolan's two-step transformation) may allow for the collection of quantitative kinetic information associated with TA-Au. In addition, it is also very important to understand why TA-Au offered the chemoselectivity with excellent stereochemistry control, while other $[L\text{-}Au]^+$ gave rapid racemization at the propargyl position with poor chemoselectivity (activation of both alkyne and allene). Herein, we report our quantitative kinetic investigation of TA-Au catalyzed propargyl ester [3,3]-rearrangement using *in situ* IR spectroscopy from a 'live' catalytic reaction.[13]



[Au]	time	yield
$IPrAuCl/AgBF_4$ (2%)	5 min	91% (**3**)
$PPh_3AuCl/AgBF_4$ (2%)	5 min	51% (**3**) + 8% (**2**)
TA-Au (1%)	8 h	95% (**2**)

Scheme 1. TA-Au as chemoselective catalyst for alkyne activation.

To acquire meaningful kinetic data for a catalytic reaction, the turnover-limiting step needs to be established. This is a challenge task for LAuCl/AgX system, giving the rapid catalyst decomposition over time. A unique advantage of TA-Au catalyst is the improved stability, which allows relatively steady concentration of the catalyst for the kinetic study. Thus, we set out to evaluate the kinetic dependence of concentration of substrate and TA-Au. The standard reaction was chosen as the model reaction for the detailed investigation (eq. 1).



(1)

To avoid the potential influence of acid (formation of HOTf), the N-Me-benzotriazole (instead of N-H) coordinated TA-Au **4** was selected.[14] The dependence of the initial rates on the concentration of TA-Au catalyst **4** was studies with varied concentrations from 0.002-0.008 M. The initial rates in different runs were calculated based on the kinetic profiles monitored by *in situ* IR. A linear relationship is established as depicted in **Figure 1**. The reaction is therefore first-order dependent on [**4**], suggesting the involvement of **4** in the turnover-limiting step.

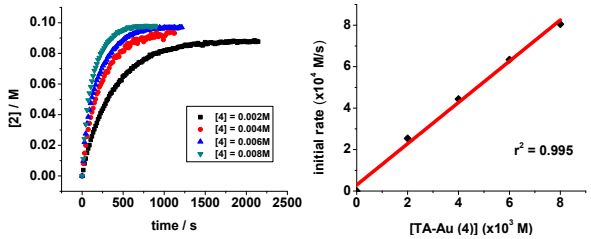


Figure 1. Dependence of the initial rates on catalyst concentrations for rearrangement of **1**. Reaction conditions: **1** (0.10 M in DCE, 1.2 mL), **4** (0.002-0.008 M in DCE), 30°C.

Subsequent experiment was to determine the kinetic order of [**1**]. Similarly, the initial rates were plotted against [**1**] varied from 0.10-0.20 M. Again, a first-order dependence was observed, as shown in **Figure 2**. Combined with two experiments, we were able to derive the rate law for this reaction: $r = k_{obs}[\mathbf{1}]^1[\mathbf{4}]^1$. According to the rate law, both the catalyst **4** and substrate **1** were involved, revealing the electronic activation of alkyne (i.e. ligand exchange) as the turnover-liming step. *In situ* monitoring of ^{31}P NMR over the entire course of reaction showed **4** as the resting state further supporting the ligand exchange as the turnover-limiting step.

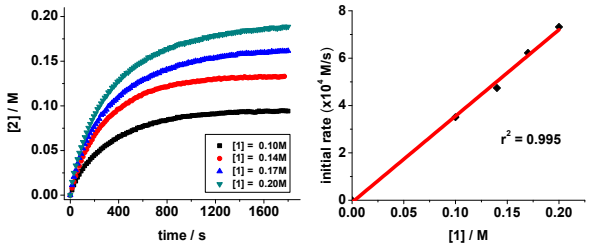
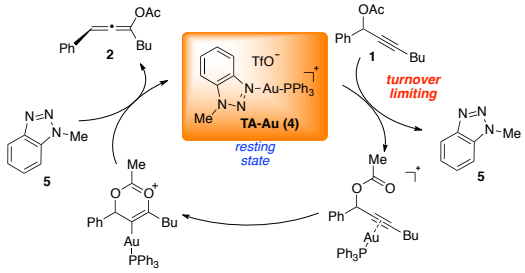


Figure 2. Dependence of the initial rates on substrate concentrations for rearrangement of **1**. Reaction conditions: **1** (0.10-0.20 M in DCE, 1.2 mL), **4** (0.003 M in DCE), 30°C.

With this kinetic data, a tentative proposed mechanism of TA-Au catalyzed propargyl ester [3,3]-rearrangement is shown in **Scheme 2**. First, the TA-Au undergoes the turnover-limiting ligand exchange with substrate to form cationic gold(I) alkyne π-complex. This complex then rapidly converts the propargyl ester to the corresponding allene. It is clear to see that the ligand exchange step significantly slows the reaction rate compared to the use of free cationic gold(I) (**Scheme 1**), which is consistent with the fact that the same reaction catalyzed by $IPrAu(L)^+$ ($L=Et_3N$, py) was also slower.[15]



Scheme 2. Proposed Mechanism for TA-Au catalyzed propargyl ester [3,3]-rearrangement

To further probe physical organic nature of this elementary step, a temperature dependent experiment was carried out in order to obtain the activation energy quantitatively. As shown in **Figure 3**, the reactions were again monitored by *in situ* IR at different temperatures (295-319 K). The activation enthalpy was determined to be 7.8 kcal/mol through Erying equation after plotting the $\ln(k_{obs}/T)$ vs. 1/T. This value reveals that ligand exchange step itself is quite a facile process at room temperature. Similarly, Echavarren reported even lower activation enthalpy values (3.7 and 6.2 kcal/mol) for his studies in the enyne cycloisomerization.[16]

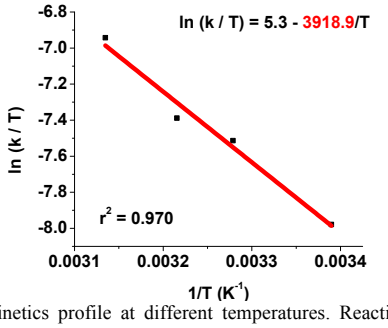
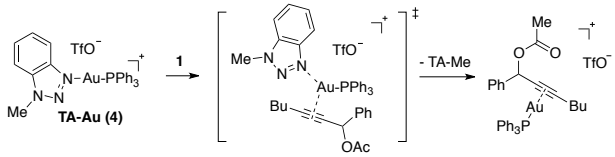


Figure 3. Kinetics profile at different temperatures. Reaction conditions: **1** (0.10 M in DCE, 1.2 mL), **TA-Au** (0.003 M in DCE), at 22, 32, 38, and 46°C.

Assumed that all the catalyst in the reaction remained active throughout the reaction, $[\mathbf{4}]_0$ will be identical to active catalyst concentration. Therefore, activation entropy was determined as -36.6 eu. The negative and relative large value supports the associative ligand substitution through a transient 3-coordinate gold(I) complex. However, the possibility of 3-coordinate gold(I) complex with TA attached as the stable intermediate cannot be ruled out at this point. Further support came from the fact that the reaction was inhibited if additional 1-methyl-benzotriazole (**5**, 4 equiv. toward TA-Au) was present. Unfortunately, we were unable to determine the exact order of [**5**] due to the extremely slow reaction rates. But a negative kinetic order of [**5**] is anticipated, which is consistent with the proposed triazole-alkyne exchange mechanism shown in **Scheme 3**.[17]



Scheme 3. Associative ligand substitution through transient 3-coordinate cationic gold(I) complex.

Finally, we prepared various TA-Au catalysts with different substituted groups benzotriazole in order to investigate the impact of the electronic nature of the TA-Au catalysts.[18] The ^{31}P NMR peaks corresponded to TA-Au catalysts provide direct information regarding the electronic nature of gold center. As expected, more electron-withdrawing group gives more upfield ^{31}P shift, suggesting the more cationic gold. The reaction kinetics is illustrated in **Figure 4**.

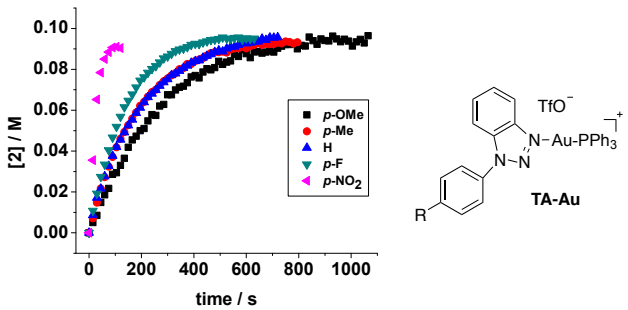


Figure 4. Kinetics profile using various TA-Au catalysts. Reaction conditions: **1** (0.10 M in DCE, 1.2 mL), **TA-Au** (0.003 M in DCE), 26°C.

Clearly, the more cationic gold(I) led to faster reaction rate. The slowest reaction was observed with 4-methoxyphenyl substituted TA-Au catalyst, however, this reaction is still faster than the reaction catalyzed by **4**, suggesting the inherent electron-withdrawing nature of the phenyl group attached to benzotriazole. The linear free energy relationship was established by plotting $\log(k/k_H)$ vs. σ_{para}, giving a ρ value of 0.74 (**Figure 5**).

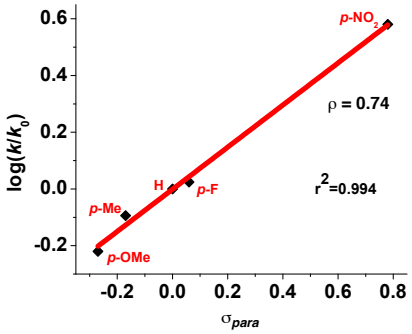


Figure 5. Hammett plot of substituted TA-Au catalysts.

The positive ρ value suggested partial positive charge building up during the reaction, which is consistent with the associative ligand substitution being the turnover-limiting step. The more electron-deficient triazole undergoes ligand exchange more rapidly, which is accounted for the faster reaction rate. This result also highlights the tunability of TA-Au catalyst. Based on the different cases, the more electron-deficient TA-Au will give shorter reaction time, while the more electron-rich TA-Au has longer catalyst lifetime.

The chemoselectivity of the TA-Au catalysts (activation of alkyne over allene) can also be explained by this ligand-substrate exchange mechanism. The DFT calculation revealed the HOMO of propargyl ester **1** is 20 kcal/mol higher than the HOMO of allene **2**.[19] Thus, the ligand exchange is much slower between allene and **TA-Au**, which supports the observed selective alkyne activation.[20]

In summary, the triazole-gold(I) complex (TA-Au) catalyzed propargyl ester [3,3]-rearrangement has been quantitatively investigated. Considering that few physical organic studies have been reported regarding gold catalyzed alkyne activation due to the poor catalyst stability and complex reaction nature, this work provided direct experimental evidences in understanding the elementary step in the TA-Au catalyzed alkyne activation. The discovery of associative ligand exchange between TA-Au and alkyne as the turnover-limiting step provided mechanistic insight, which will benefit future investigations.

Acknowledgement

We thank the NSF (CAREER-CHE-0844602 and CHE-1228336) and NSFC (No. 21228204) for financial support.

Notes and references

[a] *C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506, United Staes. Fax: 304-293-4904; Tel: 304-293-0179; E-mail: Xiaodong.Shi@mail.wvu.edu.*

[b] *Department of Medicinal Chemistry, School of Pharmacy, Shandong University, Jinan, Shandong, 250012, China, E-mail: mli@sdu.edu.cn.*

† Electronic Supplementary Information (ESI) available: [Experiment procedures, and kinetic and DFT data]. See DOI: 10.1039/b000000x/

1 (a) A. S. K. Hashmi, F. D. Toste, *Modern Gold Catalyzed Synthesis*, Wiley-VCH, Weinheim, **2012**; (b) A. S. K. Hashmi and M. Rudolph, *Chem. Soc. Rev.*, 2012, **41**, 2448; (c) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (d) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (e) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (f) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (g) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* 2007, **46**, 3410; (h) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271; (i) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed.*, 2006, **45**, 7896.

2 For recent reviews, see: (a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2010, **49**, 5232; L. Liu and G. B. Hammond, *Chem. Soc. Rev.*, 2012, **41**, 3129; (b) R. E. M. Brooner and R. A. Widenhoefer, *Angew. Chem. Int. Ed.*, 2013, **52**, 11714.

3 (a) D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962; (b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012.

4 (a) S. G. Weber, F. Rominger and B. F. Straub, *Eur. J. Inorg. Chem.*, 2012, 2863; (b) Y. Zhu, C. S. Day, L. Zhang, K. J. Hauser and A. C. Jones, *Chem. Eur. J.*, 2013, **19**, 12264.

5 A. Homs, I. Escofet, and A. M. Echavarren, *Org. Lett.*, 2013, **15**, 5782. References cited therein.

6 (a) J. Oliver-Meseguer, J. R. Cabrero-Antonino, I. Domínguez, A. Leyva-Pérez and A. Corma, *Science*, 2012, **338**, 1452; (b) J. Oliver-Meseguer, A. Leyva-Pérez and A. Corma, *ChemCatChem*, 2013, **5**, 3509.

7 W. Wang, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2012, **134**, 5697

8 For representative studies, see: (a) Z. J. Wang, D. Benitez, E. Tkatchouk, W A. Goddard III and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 13064; (b) T. J. Brown, D. Weber, M. R. Gagné and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2012, **134**, 9134.

9 (a) T. J. Brown, M. G. Dickens and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2009, **131**, 6350; (b) T. J. Brown, A. Sugie, M. G. D. Leed and R. A. Widenhoefer, *Chem. Eur. J.*, 2012, **18**, 6959; (c) R. E. M. Brooner, T. J. Brown and R. A. Widenhoefer, *Chem. Eur. J.*, 2013, **19**, 8276.

10 H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov and X. Shi, *J. Am. Chem. Soc.*, 2009, **131**, 12100.

11 (a) D. Wang, L. N. S. Gautam, C. Bollinger, A. Harris, M. Li and X. Shi, *Org. Lett.*, 2011, **13**, 2618; (b) D. Wang, X. Ye and X. Shi, *Org. Lett.*, 2010, **12**, 2088-2091.

12 (a) N. Marion, S. Díez-Gonzalez, P. Fremont, A. R. Noble and S. P. Nolan, *Angew. Chem. Int. Ed.*, 2006, **45**, 3647; and for an early example, see: (b) L. Zhang and S. Wang, *J. Am. Chem. Soc.*, 2006, **128**, 1442.

13 (a) C. He, J. Ke, H. Xu and A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 1527; (b) Z. Huang, L. Jin, H. Han and A. Lei, *Org. Biomol. Chem.*, 2013, **11**, 1810; (c) J. Li, L. Jin, C. Liu and A. Lei, *Chem. Commun.*, 2013, **49**, 9615.

14 D. Wang, Y. Zhang, A. Harris, L. N. S. Gautam and X. Shi, *Adv. Syn. Cat.*, 2011, **353**, 2584.

15 P. Nun, S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2010, **46**, 9113.

16 C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2005, **44**, 6146.

17 The inhibition could be explained by either the formation of 3-coordinate $LAu(TA)_2^+$-type complex or the competition of the external triazole ligand with alkyne substrate. Unfortunately, our attempts to detect the 3-coordinate gold complex through MS and NMR were unfruitful with no observation of any $LAu(TA)^{2+}$ type complexes. Thus, the equilibrium between TA-Au and Au-alkyne π-complex is the likely explanation for the observed decreased reaction

rate when external TA ligands were used. Detailed derivation of rate law is provided in supporting information.
18 K. Wang, M. Chen, Q. Wang, X. Shi and J. K. Lee, *J. Org. Chem.*, 2013, **78**, 7249.
19 DFT calculation was performed on Gaussian 03 program at the B3LYP/6-311G level of theory.
20 P. Nun, S. Gaillard, A. Poater, L. Cavalloc and S. P. Nolan, *Org. Biomol. Chem.*, 2011, **9**, 101.