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1,2,3-Triazole Bound Au(I) (TA-Au) as Chemoselective Catalysts in Promoting Asymmetric Synthesis of Substituted Allenes

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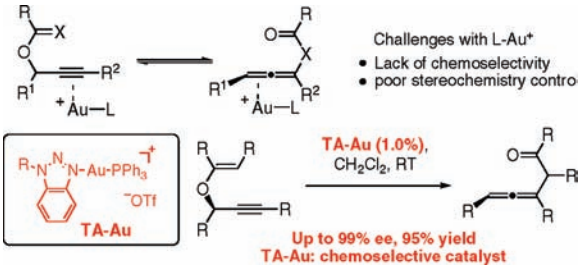
ABSTRACT



The triazole-Au (TA-Au) complexes were identified as effective chemoselective catalysts in promoting propargyl ester/ether 3,3-rearrangements. The highly reactive allenes, which could not be isolated by simple cationic gold catalysts, were prepared in excellent yields (1% catalyst loading, >90% yields). Unlike other reported Au catalysts, the TA-Au provided effective chirality transfer without racemization over a long period of time, giving enantioenriched allenes with excellent stereoselectivity (1% catalyst loading, up to 99% ee).

One aspiration for synthetic chemists is to develop new methods that account for effective chemo-, regio-, and stereoselective transformations.[1] The Au catalyzed propargyl ester rearrangement was considered as one of the most important reaction modes in the recent surge of homogeneous gold catalysis.[2,3] With support from recent mechanistic studies, it became clear that this transformation occurred through a 3,3-rearrangement.[4] Moreover,

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(3) For selected recent publications, see: (a) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859. (b) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674–8679. (c) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373. (d) Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350–6351.

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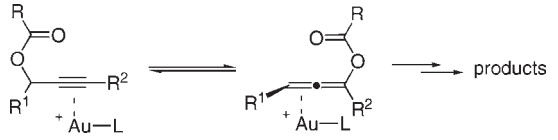
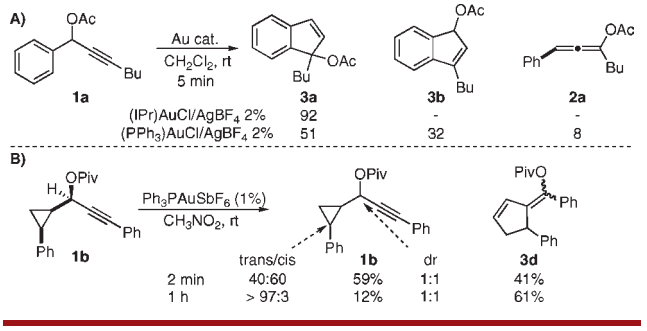
both experimental and theoretical investigations confirmed the reversibility between allene and propargyl ester (Scheme 1), which led to a considerable challenge: how to achieve chemoselective activation of alkyne over allene.

Scheme 1. A Challenge in Cationic Au Catalysis: How to Achieve Chemoselective Activation of Alkyne over Allene?



According to the literature, the current strategy for applications of gold catalyzed 3,3-rearrangement was the introduction of proper reaction partners to trap the Au-activated allene intermediates. The indene synthesis reported by Nolan and co-workers[5] along with the cyclopropanyl propargyl ester rearrangement[6] reported by Toste and co-workers[7] are two examples that highlight the power of this transformation in complex molecule synthesis (Scheme 2).

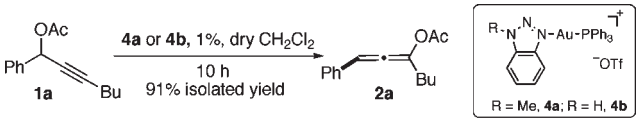
Scheme 2. Trapping the Allene by Proper Synthetic Partners



However, the lack of chemoselectivity by cationic Au catalysts generated significant limitations for this transformation: (a) although functional allenes were important building blocks in organic synthesis, the Au catalyzed 3,3-rearrangement was not considered as a practical approach for allene synthesis due to the good reactivity of the Au activated allene toward many other groups (even a simple benzene ring, Scheme 2A); (b) the rapid equilibrium between alkyne and allene under the reaction conditions caused poor stereoselectivity due to the rapid racemization on the propargyl stereogenic center (Scheme 2B; complete racemization at the propargyl position occurred in 2 min). Therefore, effective new catalytic systems that can achieve selective alkyne activation over allene are highly desirable. Herein, we report the triazole coordinated PPh_3Au^+ complexes as chemoselective catalysts to achieve good selectivity in activating alkyne over allene, which allowed the effective synthesis of highly reactive allene esters in excellent yields (1% loading, up to 95% yields). In addition, through chirality transfer, asymmetric synthesis of substituted allenes was achieved using these simply modified triazole Au(I) catalysts with excellent stereoselectivity (up to 99% ee).

Our interest in developing 1,2,3-triazoles[8] as new ligands to adjust transition metal reactivity[9] has led to the recent discovery of 1,2,3-triazole-Au (TA-Au) complexes **4**.[10] These complexes showed significantly improved thermal and substrate stability in addition to good reactivity toward alkyne.[11] One particularly interesting result was the TA-Au catalyzed synthesis of kinetically favored *E*-α-haloenones, which suggested that the TA-Au catalysts did not interrupt the allene reactivity.[12] Encouraged by this result, we decided to investigate whether the triazole-Au complexes could be applied as effective chemoselective catalysts for propargyl ester 3,3-rearrangement. The reactions of **1a** were set up with TA-Au as the catalysts. The results are shown in Scheme 3.

Scheme 3. Proposed S_N2' Addition Mechanism by Nolan



time	indene **3a**	indene **3b**	**2a**	time	indene **3a**	indene **3b**	**2a**
10 min	0	0	15%	20 h	0	0	>98%
4 h	0	0	83%	48 h	0	0	>98%
8 h	0	0	95%				

As shown in Scheme 3, both **4a** and **4b** catalysts indicated good reactivity toward alkyne activation, promoting the 3,3-rearrangement with high efficiency (1% loading). Impressively, excellent chemoselectivity was achieved, where no further reactions proceeded, giving the desired allene

(5) (a) Marion, N.; Díez-Gonzalez, S.; Fremont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647–3650. (b) Marion, N.; Carlqvist, P.; Gealageas, R.; Fremont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437–6451.

(6) See reviews: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50. (c) Hiersemann, M.; Abraham., L. *Eur. J. Org. Chem.* **2002**, 1461–1471. For propargyl ether rearrangement, see:(d) Grissom, J. W.; Kilingberg, D.; Huang, D.; Slattery, B. *J. Org. Chem.* **1997**, *62*, 603–626.

(7) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. (b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133. (c) Mauleon, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *1131*, 4513–4520.

(8) (a) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493–1496. (b) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254–3256. (c) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389–5392. (d) Duan, H.; Yan, W.; Sengupta, S.; Shi, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3899–3902. (e) Yan, W.; Wang, Q.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2010**, *12*, 3308–3311.

(9) (a) Duan, H.; Sengupta, S.; Petersen, J. L.; Shi, X. *Organometallics* **2009**, *28*, 2352–2355. (b) Liao, W.; Chen, Y.; Duan, H.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2009**, 6436–6438. (c) Chen, Y.; Wang, D.; Petersen, J. L.; Akhmedov, N.; Shi, X. *Chem. Commun.* **2010**, *46*, 6147–6149.

(10) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.

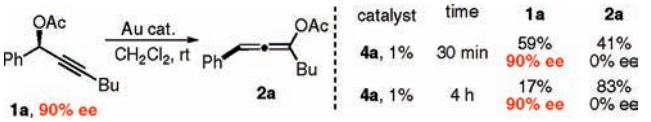
(11) Chen, Y.; Yan, W.; Akhmedov, N.; Shi, X. *Org. Lett.* **2010**, *12*, 344–347.

(12) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088–2091.

products in excellent yields. This simple modification of catalysts provided one effective strategy in the preparation of functional allenes.

Encouraged by the good chemoselectivity, we then wondered whether TA-Au could be used as an effective catalyst for the stereospecific transformation by overcoming the rapid racemization associated with other reported cationic Au catalysts. In particular, could TA-Au catalysts help to achieve the asymmetric synthesis of chiral allenes by effective chirality transfer from enantiomeric enriched propargyl alcohols (readily available). The example shown in Scheme 2B highlighted the challenges for this proposed chirality transfer: rapid epimerization on the propargyl position (2 min) due to the Au activation of allene caused a loss of stereochemistry at the propargyl position. To investigate the chirality transfer, enantiomeric enriched **1a** was first used to react with TA-Au **4a** (Scheme 4).

Scheme 4

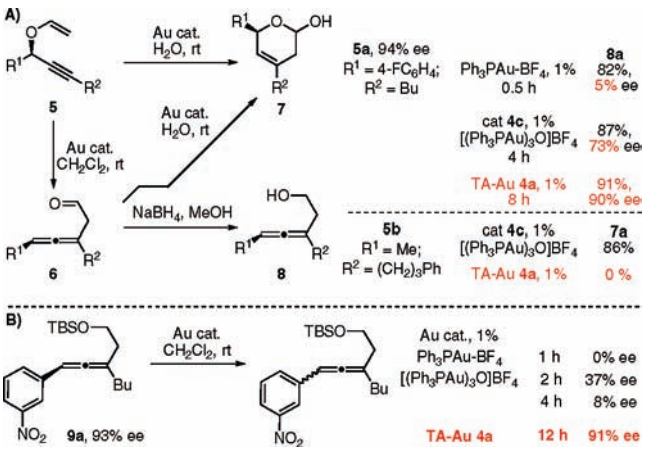


Unfortunately, allene **2a** was obtained as racemic mixtures (0% ee) even with TA-Au as the catalyst at low temperature (−40 °C). However, a closer look of this reaction revealed a rather surprising observation: no epimerization of propargyl ester occurred during the reaction, which strongly suggested the lack of equilibrium between allene **2a** and propargyl ester **1a** while TA-Au catalysts were used. The loss of allene **2a** stereochemistry was likely caused by the low energetic barrier for the allene racemization process (no enantiomeric enriched allene acetates have ever been reported). This hypothesis was supported by the DFT computational studies, where the relative low energy barrier (5 kcal/mol) was revealed between the two resonance structures of allene acetate.[13]

Considering the promising chemoselectivity from the TA-Au catalyst, we postulated that asymmetric synthesis of allenes could be achieved if the resulting allenes have a high epimerization barrier. To verify this hypothesis, propargyl-vinyl-ether **5a** was prepared for the chirality transfer investigation. As expected, excellent chirality transfer was obtained with propargyl vinyl ether **5a** while TA-Au was used (1% catalyst, Scheme 5A).

It has been reported that gold-oxo complex $[(Ph_3PAu)_3O]BF_4$ **4c** could also promote this reaction with good to modest yields and good chirality transfer.[7a] However, this complex was not a chemoselective catalyst. As demonstrated

Scheme 5

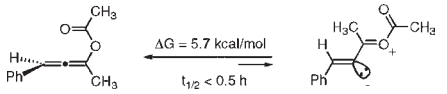


in Scheme 5B, treating the allene **9a** with the gold-oxo catalyst over time resulted in significant racemization of the allenes. As a result, the gold-oxo catalyst **4c** suffered from the limited substrate scope, where significantly different reaction rates between alkyne activation and allene racemization were required to ensure the chirality transfer. Overall, the gold-oxo complexes were the precatalysts, which could slowly release the L-Au^+ catalysts. Therefore, it adopted the similar reactivity of the L-Au^+ catalysts. This lack of chemoselectivity with gold-oxo catalysts was further demonstrated by the synthesis of dihydropyran **7** from intramolecular trapping of gold activated allenes (Scheme 5A).[7b] This reaction, despite providing very attractive new synthetic methods, highlighted the strong desire for a "true" chemoselective gold catalyst. The TA-Au catalyst not only could effectively promote this transformation with excellent chirality transfer but also successfully avoid the undesired racemization of allene **9a** over a long period of time (12 h, Scheme 5B). To the best of our knowledge, this result revealed TA-Au as the first successful chemoselective catalyst, selectively activating alkyne over allenes, which would likely further extend the reaction scope for fast growing homogeneous gold catalysis research.

To explore the reaction substrate scope, various chiral propargyl vinyl ethers were prepared. The results are summarized in Figure 1.

As shown in Figure 1, TA-Au was an effective catalyst for a large scope of substrates. Both terminal and internal alkynes were suitable for this transformation, giving the

(13) The DFT computational studies were carried out by the Gaussian 03 program to a B3LYP/6-311G level. See details from Supporting Information.



(14) The substrates generally favoured 2,3-migration over 3,3-migration. Therefore, a stepwise 2,3-migration was one possible mechanism, which accounts for the loss of stereochemistry information. Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.

(15) During the preparation of this manuscript, Nolan and coworkers reported the application of amine and pyridine modified Au catalysts for the allene synthesis. Nun, P.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 9113–9115. This interesting work provided another example of a neutral coordination ligand in tuning the Au(I) catalyst reactivity. However, no chirality transfer was reported. Our recent brief screening with that catalyst indicated quick racemization at the propargyl position (similar to other cationic gold), which further highlighted the unique reactivity of the TA-Au catalyst.

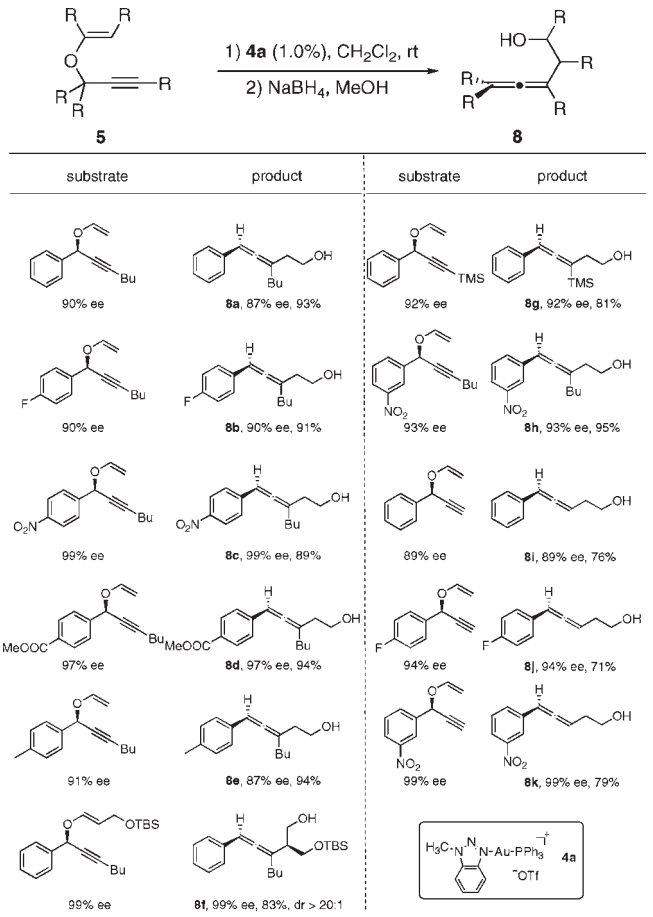


Figure 1. Reaction substrate scope for chiral allenes. General reaction conditions: **5** (0.25 mmol), **4a** (1.0%), DCM (2.5 mL), The reactions were monitored by TLC (0.5−12 h), rt; ee was determined by HPLC. For products **8i**−**j**, **4a** (3.0%) was used.

allene products in good to excellent yields. Effective chirality transfers were observed in terminal alkynes and alkyl substituted internal alkynes. The excellent diastereoselectivity obtained in **8f** suggested a chairlike transition state in the rearrangement.[7a] Racemic allenes were obtained with phenyl substituted internal alkynes, which implied possible higher reactivity or a different mechanism[14] for these substrates. Nevertheless, the high efficiency and good stereoselectivity made the reported strategy one practical approach for the asymmetric synthesis of chiral allenes. It was worth noting that the true chemoselectivity reaction nature of the TA-Au catalysts opened the possibility for the development of new reactions that could take advantage of the good reactivity of a gold cation toward alkyne activation without suffering the undesired sequential allene activation by the same catalyst.

In conclusion, we report herein the application of 1,2,3-triazole Au (TA-Au) complexes as chemoselective catalysts for propargyl ester/ether rearrangements. Excellent yields of allenes were obtained.[15] This method was applied to the synthesis of chiral allenes, giving good yields and excellent chirality transfer. The interesting new reactivity by TA-Au not only provided an efficient strategy for the synthesis of enantioenriched allenes, which were challenging using other methods, but also, more importantly, revealed TA-Au complexes as a new class of catalysts in promoting alkyne activation with different reactivity than the L-Au$^+$ catalysts, which would likely benefit from the discovery of new efficient organic transformations.

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