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Efficient Synthesis of *E*-α-Haloenones Through Chemoselective Alkyne Activation Over Allene with Triazole−Au Catalysts

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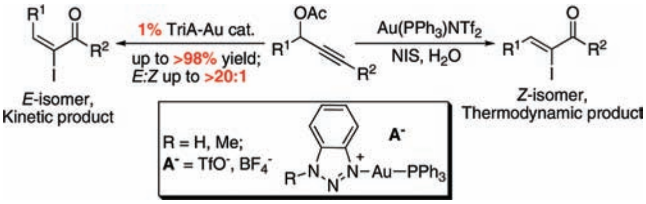
ABSTRACT



The *E*-α-haloenones were prepared through a triazole−Au complex (TriA−Au) catalyzed propargyl acetate rearrangement and sequential allene halogenation. The reactions proceeded with only 1% catalyst loading, giving the challenging kinetic products in excellent yields and good to excellent stereoselectivity. These results not only provided the first example for the synthesis of challenging kinetic *E*-haloenones, but also revealed triazole−Au complexes as effective catalysts in promoting chemoselective activation of alkynes over allenes.

The motivation for chemists to develop new synthetic methodologies is to find effective solutions for challenging functional group transformations, especially those with good chemo-, regio-, and stereoselectivities.[1] Within this context, selective synthesis of kinetic products from their thermodynamically stable partners is challenging and attractive. Herein, we report the efficient synthesis of *E*-α-haloenones from triazole−gold (TriA−Au)[2] catalyzed propargyl acetate rearrangement in the presence of NXS. It is important to notice that by simply using the triazole as the "X-factor"[3] in Au coordination, good chemoselectivity was achieved, where cationic Au catalyst activated alkynes without influencing the reactivity of electron-enriched allenes.

The first decade of the 21st century evidenced the extremely fast growth of homogeneous Au catalysis.[4] Both Au(I) and Au(III) cations indicated great reactivity toward C−C multiple bonds, especially for alkynes and allenes. On the basis of this unique property, numerous new reactions have been developed in the last several years to facilitate complex functional group transformations.

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[1] For some recent reviews, see: (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724. (b) Lyons, T.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227–3274. (d) Díez-González, S.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 349–358. (e) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.

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

[3] Chen, Y.; Yan, W.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2010**, *12*, 344–347.

[4] 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. (j) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.

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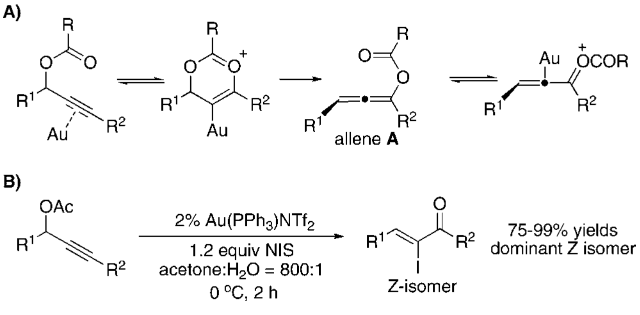
Scheme 1. Au-Catalyzed Propargyl Acetate Arrangements



One interesting gold-mediated transformation was the propargyl acetate arrangement as shown in Scheme 1A. As readily available starting materials, the propargyl acetate could undergo 1,3-migration with the presence of Au catalysts,[5] giving the corresponding allene ester **A**.

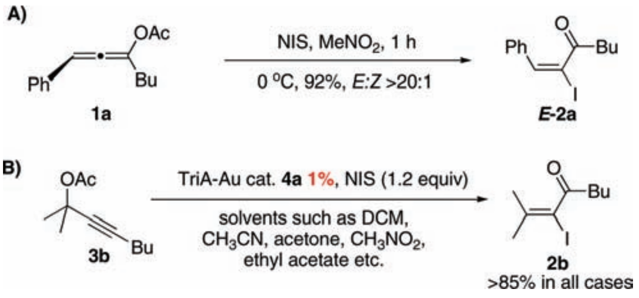
Although this migration was widely accepted as the key step in the Au-catalyzed propargyl acetate activation, allene **A** has not been successfully isolated with good yields under the reaction conditions.[6] This is due to the fact that cationic Au catalysts can also activate allene to give active intermediate, which may undergo different reaction paths. Using this strategy, different cascade-type reactions have been developed by introducing proper reactants to react with gold-activated allene. One example is the synthesis of *Z*-α-iodoenones recently reported by Zhang and co-workers (Scheme 1B).[7]

Through condition screening, the authors revealed that the reactions gave good to excellent yields in mixed solvents (acetone:H_2O = 800:1) with the thermodynamically stable *Z*-isomer as the dominant products. Notably, the composition of solvents appeared crucial for good reaction performance, where mixed solvents such as acetone/H_2O = 40:1 gave only 35% yields. This cascade reaction is attractive since it gives the α-iodoenones, which are important synthetic intermediates and can be readily converted into many different vinyl compounds through metal-mediated cross coupling.[8]

However, there was one mechanistic concern regarding the product stereochemistry: while the R^1 group blocks one side of the allene, the iodination should occur from the opposite site of R^1, giving the kinetically favored *E*-isomers. The authors later proposed the Au activation of allene esters to explain the observed dominant *Z*-selectivity.[7c] Giving the importance of vinyl halide products in organic synthesis, we were interested in pursuing the possibility to achieve the challenging *E*-isomers.

While the hypothesis for the observed *Z*-selectivity was associated with Au activation of allenes, we first evaluated the stereoselectivity in the iodination of allenes. The allene ester **1a** was prepared by using a literature reported method[6] to react with NIS (Scheme 2A). As expected, the kinetically favored *E*-isomer was obtained as the major product, which supported the hypothesis that Au activation of allene **1a** was likely the reason for the formation of *Z*-isomer when $(PPh_3)AuNTf_2$ was used as the catalyst.

Scheme 2. Formation of Kinetically Favored *E*-Isomers



Recently, we reported the synthesis and characterization of triazole-coordinated cationic Au(I) complexes as new catalysts in the alkyne activation.[2,9] The key feature of these new catalysts was to provide effective dynamic binding between 1,2,3-triazole and gold cations, which helped the stability of the gold catalysts without significantly decreasing their reactivity.[3] We wondered whether triazole−Au (TriA−Au) could be an effective catalyst in promoting this cascade vinyl-iodination reaction. The propargyl acetate **3b** was then used to react with NIS in the presence of triazole−Au catalyst. To our delight, the TriA−Au promoted this reaction with high efficiency and an excellent yield of vinyl-iodide **2b** was received with only 1% catalyst loading. Notably, compared with the previously reported $Ph_3PAuNTf_2$ catalyst, no special solvent mixture was required when triazole−Au catalyst was used and excellent yields of the desired products **2b** were received in various solvents (Scheme 2B). Encouraged by this result, we then investigated the *Z*/*E* selectivity of this cascade process. The propargyl acetate **3a** was prepared to

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(5) For 1,3-shifts, see: (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443. (c) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957–1959. (d) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585–4587. (e) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414–8415. (f) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615. (g) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274–14275.

(6) Marion, N.; Carlqvist, P.; Gealageas, R.; Fremont, P.; Maseras, F.; Nolan, S. P. *Chem.*−*Eur. J.* **2007**, *13*, 6437–6451.

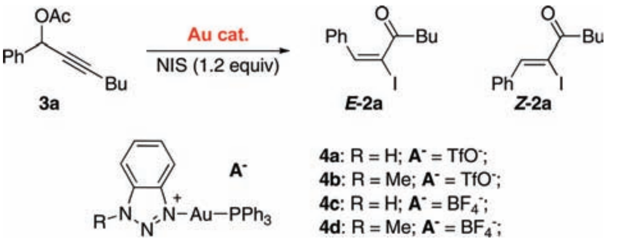
(7) (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147–2150. (b) Ye, L.; Zhang, L. *Org. Lett.* **2009**, *11*, 3646–3649. (c) Yu, M.; Zhang, G.; Zhang, L. *Tetrahedron* **2009**, *65*, 1846–1855.

(8) For a review, see: Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179–194.

(9) See recent examples in triazole bound metal complexes see: (a) Liao, W.; Chen, Y.; Duan, H.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2009**, 6436–6438. (b) Duan, H.; Sengupta, S.; Petersen, J. L.; Shi, X. *Organomatellic* **2009**, *28*, 2352–2355. See the following for recent developments for the preparation of substituted triazoles: (c) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493–1496. (d) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254–3256. (e) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389–5392. (f) Duan, H.; Yan, W.; Sengupta, S.; Shi, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3899–3902.

react with NIS in the presence of TriA−Au **4** catalysts. The results are summarized in Table 1.

Table 1. Screening of Reaction Conditions[a,e]



	catalyst	loading (%)	solvents	temp (°C)	time (h)	yield (%)[b]	E/Z[c]
1	**4a**	2.0	wet CH_2Cl_2	rt	1	>98	7.0:1
2	**4b**	2.0	wet CH_2Cl_2	rt	1	95	5.0:1
3	**4c**	2.0	wet CH_2Cl_2	rt	1	96	5.7:1
4	**4d**	2.0	wet CH_2Cl_2	rt	1	89	6.3:1
5	**4a**	1.0	wet CH_2Cl_2	rt	2	>98	7.0:1
6	**4a**	1.0	wet $MeNO_2$	rt	2	>98	12:1
7	**4a**	1.0	wet acetone	rt	2	94	11:1
8	**4a**	1.0	wet CH_3CN	rt	2	90	9.0:1
9	**4a**	1.0	wet EtOAc	rt	2	>98	10:1
10	**4a**	1.0	wet $MeNO_2$	0	10	93[d]	>20:1
11	**4a**	1.0	wet EtOAc	0	10	>98	15:1
12	**4a**	1.0	wet acetone	0	10	89	17:1
13	**4a**	1.0	wet CH_2Cl_2	0	10	88	15:1
14	**4a**	1.0	wet CH_3CN	0	10	86	10:1

[a] General reaction conditions: **3a** (0.25 mmol, 1.0 equiv) and NIS (1.2 equiv), monitored by TLC. [b] Yields determined by NMR with 1,3,5-trimethoxybenzene as internal standard. [c] r®atio determined by NMR of crude reaction mixtures. [d] Isolated yield. [e] Various amounts of water have been investigated and results are shown in ref 10.

It has been reported by Nolan and co-worker that **3a** could undergo the intramolecular hydroarylation in the presence of 2% $Ph_3PAuCl/AgBF_4$ in DCM, giving substituted indenes in modest yields (51%, 5 min).[11] This was confirmed by the experimental observation where the reaction of **3a** and NIS gave complex mixtures along with Au(I) catalyst decomposition in 30 min when 2% $Ph_3PAuCl/AgOTf$ was used as the catalyst.

Impressively, similar to the alkyl-substituted propargyl acetate **3b**, reactions of **3a** and triazole−Au **4** gave very clean reactions and, more importantly, the kinetically favored *E*-isomer was obtained as the major product. These precatalysts were very efficient and near-quantitative yields were obtained with only 1% catalyst loading. Moreover, the counteranions and the acidic proton on the triazole showed little influence regarding the performance and selectivity (entries 1−4). Screening of solvents revealed that nitro methane gave the best stereoselectivity (entries 6−9). Lowering the reaction temperature to 0 °C provided the optimal reaction conditions, where the *E*-isomer was produced in excellent yields (entry 10). Considering the high *E*-selectivity for the allene iodination shown in Scheme 2A, these results indicated that triazole−Au complexes were effective precatalysts with outstanding chemoselectivity: *effective activation of alkynes without influencing the reactivity of the allenes*. With this new method in hand, representative propargyl acetates were prepared to investigate the reaction substrate scope. The results are summarized in Figure 1.

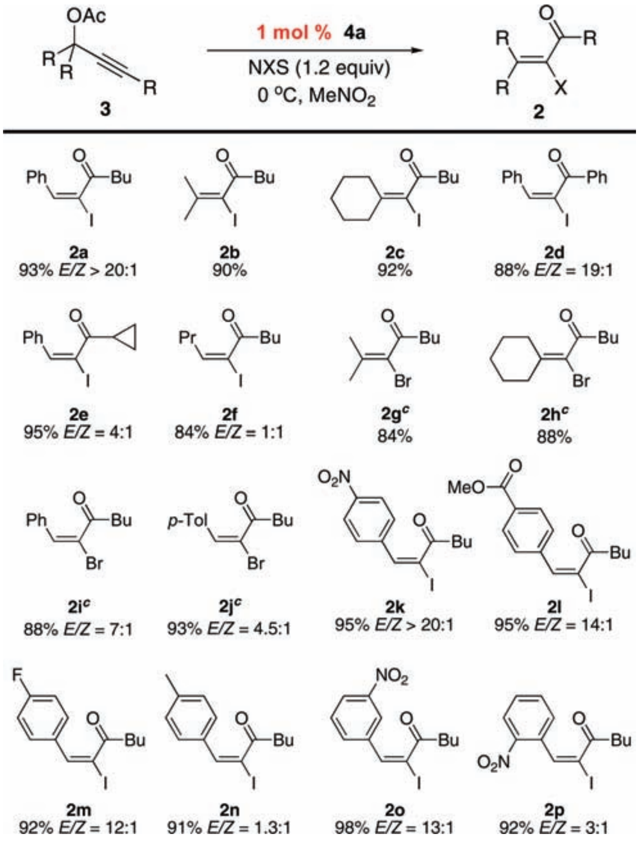


Figure 1. Reaction substrate scope. (a) General reaction conditions: **3** (0.25 mmol, 1.0 equiv), NXS (1.2 equiv), **4a** (1.0 mol %), and $MeNO_2$ (2.5 mL), monitored by TLC. (b) *E*:*Z* ratio determined by NMR of crude reaction mixtures. (c) Reactions proceeded at room temperature.

As shown in Figure 1, both aliphatic-substituted alkynes and aromatic-substituted alkynes were suitable for this transformation. Notably, this reaction did not work for the terminal alkyne since the 1,2-rearrangement was usually preferred for terminal alkyne propargyl acetate.[12] The reaction could also tolerate both alkyl- and aryl-substituted groups on the acetate side, giving excellent yields in all cases. NBS was suitable for this transformation, giving the corre-

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[10] Reagents and conditions: 1.0 equiv of H_2O in dry DCM gave 89% yield in 2 h; 2.0 equiv of H_2O in dry DCM gave 94% yield in 2 h; 10 equiv of H_2O in dry DCM gave 91% yield in 2 h. A 7:1 *E*:*Z* ratio was observed in all cases.

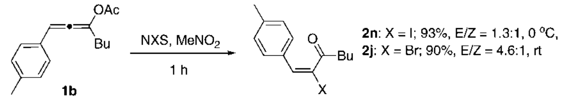
[11] Marion, N.; Díez-Gonzalez, S.; Fremont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647–3650.

[12] The triazole−Au promoted terminal alkyne propargyl acetate rearrangement is currently under investigation. The result will be reported in due course.

sponding vinyl bromide, which further extended the reaction substrate scope. NCS did not work in this reaction, which was likely caused by the decreased reactivity of the electrophile. Compared with previously reported Au catalysts, the triazole−Au complexes promoted this transformation with much improved efficiency, broader substrate scope, and more practical reaction conditions (no need for careful solvents control).

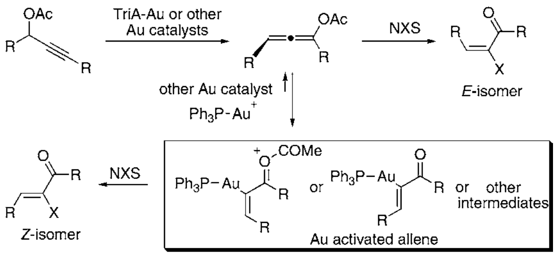
Different substitution groups showed great influences on the double bond stereoselectivity. For substrates with phenyl and electron withdrawing group substituted benzenes, excellent *E*-selectivity was received. To the best of our knowledge, this is the first example for the synthesis of kinetically favored α-haloenones. However, the *E*-isomer selectivity decreased significantly in the alkyl-substituted substrates, which was likely caused by the poor stereoselectivity between electron-enriched allenes and NIS electrophile. This hypothesis was supported by the observation in *o*-nitro-substituted benzene **2p**, where low *E*-selectivity was received, which was likely caused by the nitro-directing effect for the cis-iodination. To test our hypothesis, a reaction between toluene-substituted allene and NIS was performed (Scheme 3). As expected, similar poor *E*/*Z* selectivity was obtained.

Scheme 3. Lack of *E*/*Z* Selectivity of Electron-Enriched Allene



This result provided strong support for our hypothesis that the triazole−Au complexes, unlike other cationic Au(I) catalysts, provided a unique class of precatalysts that selectively activated alkyne without influencing the reactivity of the allene acetate intermediates (Scheme 4).

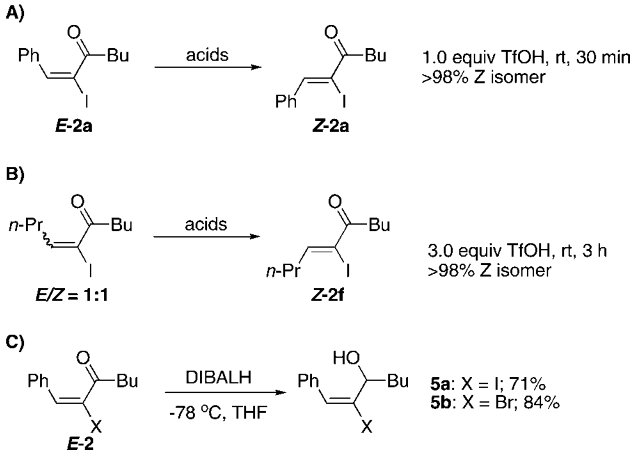
Scheme 4. Proposed Reaction Mechanism



As reported in our previous studies, the key function of 1,2,3-triazole ligands was to provide effective dynamic coordination with the Au(I) cation. Through this coordination, the actual Au catalyst (Ph_3PAu^+ in this case) was stabilized from decomposition. The observed excellent chemoselectivity of triazole−Au in this cascade reaction could be caused by the competition between the triazole ligands and the vinyl−Au intermediates (note: addition of excess 1,2,3-triazoles gave a slower reaction rate due to the low concentration of active Ph_3PAu^+). More mechanistic studies regarding triazole−Au promoted propargyl acetate rearrangement are currently underway.

While the reported method gave the challenging *E*-isomers in good yields, these kinetic products could be readily transferred into thermodynamically stable *Z*-isomers by treating with acids (Scheme 5A,B). This stereochemistry conversion could be avoided through enone reduction to the corresponding allylic alcohol (Scheme 5C). Excellent stereochemistry retention was achieved, giving the corresponding vinyl iodide and vinyl bromide in good yields.[13]

Scheme 5



In summary, the triazole−Au complexes were revealed as effective precatalysts in promoting propargyl acetate rearrangement in the presence of NXS. The catalysts were efficient to give >90% yields with only 1% loading. Unlike other gold catalysts, the triazole−Au complexes effectively promoted the formation of challenging kinetic *E*-isomers with good to excellent selectivity. These results indicated the excellent chemoselectivity of these triazole−Au catalysts. It is expected that this unique property from triazole−Au complexes could lead to the discoveries of other attractive transformations by producing stable, in situ formed highly reactive allenes.

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

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(13) The proposed vinyl−gold intermediateds have been suggested in literature (ref 7) and not been proved yet.