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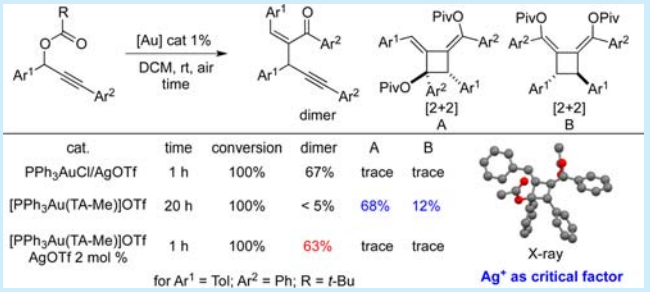
Ambient Intermolecular [2 + 2] Cycloaddition: An Example of Carbophilicity and Oxophilicity Competition in Au/Ag Catalysis

Yijin Su, Yanwei Zhang, Novruz G. Akhmedov, Jeffrey L. Petersen, and Xiaodong Shi*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

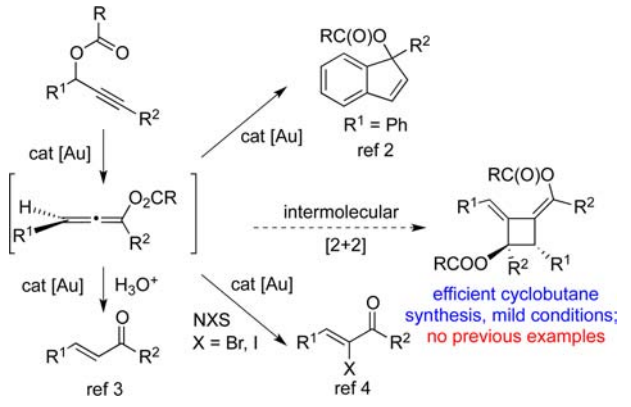
Supporting Information

ABSTRACT: The gold-catalyzed intermolecular [2 + 2] cycloaddition of propargyl esters was achieved with good stereoselectivity. The "silver-free" condition was critical for this transformation, while only a trace amount of [2 + 2] products were formed in the presence of silver under otherwise identical conditions.



The gold-catalyzed propargyl ester rearrangement has been well studied during the past decade, both experimentally and computationally.[1] The reactions typically undergo 3,3-rearrangement via gold promoted alkyne activation. The allene intermediates can be further activated by the same gold catalysts and translated into various products, such as indenes,[2] enones,[3] and vinyl halides[4] (Scheme 1). Recently, special gold

Scheme 1. Gold-Catalyzed Propargyl Ester Activation



catalysts have been reported to achieve high yields of allene intermediates, including the triazole gold reported by our group.[5] While this chemistry seems well understood, one "concealed" problem was that most of these transformations generally lack tolerance for the diaryl substituted internal alkynes (R^1, R^2 = aryl groups). For example, simply treating diphenyl propargyl ester **1a** (R^1 = R^2 = Ph, R = CH_3) with various LAuCl/AgX (L = PPh_3, IPr, XPhos; X = TfO^-, Tf_2N^-, SbF_6^-, BF_4^-) catalysts gave complex reaction mixtures with little indene or allene obtained. To fill this missing piece of the puzzle, we conducted detailed investigations on this specific type of substrate. Herein, we report the different products formed from this diaryl propargyl ester rearrangement and the intermolecular allene [2 + 2] cycloaddition at rt. In addition, the "silver-free" condition is critical in this transformation: in the presence of silver, even a catalytic amount, dimer **2** was observed over the [2 + 2] products due to the silver-activated substitution. Considering the extensive efforts from various research groups toward understanding the role of silver in gold catalysis,[6] this work provides another type of silver influence as an oxophilic Lewis acid, which deviates from the gold reaction pathway.

The cationic gold complexes are effective carbophilic π-acids, which can effectively activate both an alkyne and allene.[7] According to literature, three types of chemoselective gold catalyst (activate alkyne over allene) have been reported as gold-oxo complexes,[8] gold-pyridine/Et_3N complexes,[9] and gold-1,2,3-triazole complexes (TA-Au).[10] Surprisingly, among all the reported gold-catalyzed propargyl ester rearrangements, diaryl propargyl esters are not viable substrates. In fact, during our investigations on triazole-gold (TA-Au) catalyzed allene synthesis, complex reaction mixtures were observed. To understand how this particular type of substrate reacts, we monitored the reactions of compound **1a** with various gold catalysts (Figure 1).

First, treating **1a** with LAuCl/AgX (5% loading, L = PPh_3, IPr, XPhos, X = OTf, NTf_2 or SbF_6) gave complex reaction mixtures. Through careful examination, dimer **2a** was identified as the major product (50% yield using anhydrous solvent; see detailed structure analysis in the Supporting Information). With the triazole gold (TA-Au) catalysts, the reaction was much cleaner (less polymerization and decomposition). However, in addition to the dimer **2a** (30%), several other products were observed. Fortunately, the structure of one major product was

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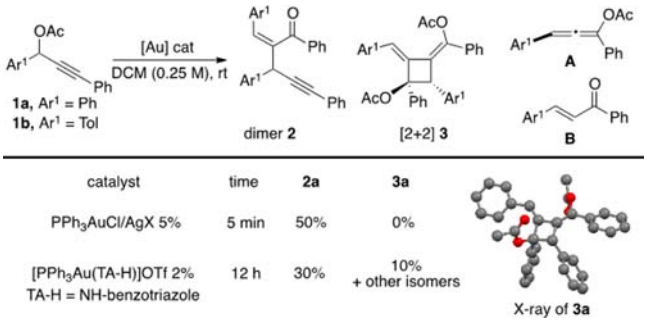
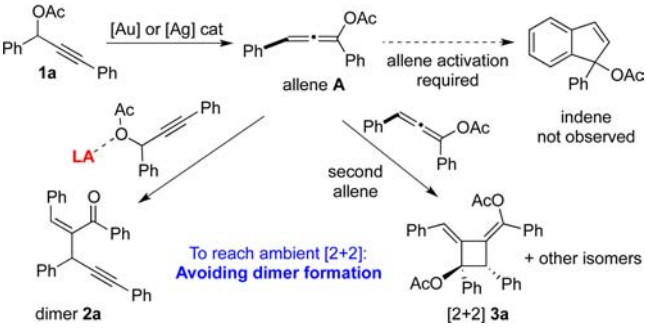


Figure 1. Analyzing the propargyl rearrangement of **1a**.

determined by X-ray crystallography as the [2 + 2] cycloaddition product **3a**. Other minor products were identified as the stereoisomers generated from the [2 + 2] cycloaddition.

This result was exciting since it was the first example of an intermolecular allene [2 + 2] reaction through propargyl ester rearrangement. Notably, indene was not observed in this case. The successful confirmation of the dimer and the [2 + 2] cycloaddition products greatly enhance our understanding of this reaction. A proposed reaction mechanism is shown in Scheme 2.

Scheme 2. Propargyl Ester Activation

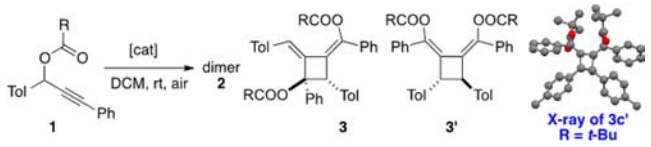


Cyclobutanes are very attractive building blocks in organic synthesis, and this reaction is conducted under mild conditions (rt) from simple starting materials. Thus, the discovery shown above revealed an interesting new approach to access substituted cyclobutanes under mild conditions. As shown in Scheme 2, the allene should be formed prior to either dimerization or cyclization. This was confirmed by monitoring the reaction with NMR: allene **A** was the only product formed during the first 2 h of reaction when treating **1a** with TA-Au catalysts. Efforts to isolate allene **A** were unsuccessful due to the poor stability. To improve the chemoselectivity ([2 + 2] over dimer) and stereoselectivity (different cyclobutane isomers), we prepared various propargyl ester derivatives and charged them under gold catalytic conditions. The results are summarized in Table 1.

The $PPh_3AuCl/AgOTf$ catalysts gave only dimer **2** with no cycloaddition product **3** observed (entry 1). The silver-free TA-Au catalyst produced the desired [2 + 2] products as mixtures of isomers. With the NH-triazole (TA-H) as ligand, 43% dimer was obtained (entry 2). The amount of dimer was decreased when *N*-methyl triazole (TA-Me) was used (entry 3), likely caused by the elimination of an acidic proton on NH-triazole (activating OAc leaving group). Switching acetate to benzoylate resulted in the exclusive formation of a dimer due to the better propargyl leaving group ($PhCOO^-$ vs CH_3COO^-). Finally, application of pivalate achieved excellent chemoselectivity, giving the [2 + 2] products in good yields (>85% combining all isomers, entry 5). Moreover, the bulky pivalate group also gave significantly improved stereoselectivity with only two major cycloaddition products obtained (**3** and **3′**) in a 5:1 ratio. The structure of the minor isomer, **3′**, was also confirmed by the X-ray crystallography. The silver-free gold oxo catalyst $[(PPh_3Au)_3O]OTf$ could also promote this reaction effectively (entry 6), though with a slightly lower reaction rate compared with that using TA-Au.

Silver salt was crucial in this transformation. As shown in entry 7, the addition of 2% AgOTf led to the formation of only dimer **2** without any cycloaddition product **3** obtained. Using a silver catalyst alone (entry 8) gave the same dimer product with a slower reaction rate, likely due to the decreased reactivity of

Table 1. Optimization of Gold(I)-Catalyzed Allene [2 + 2][a]



						yield (%)[b]			
entry	cat. (%)	R	temp (°C)	time (h)	conv (%)[b]	**2**	**3**	**3′**	other isomer
1	$PPh_3AuCl/AgOTf$ (5%)	CH_3	rt	1	100	67	trace	trace	–
2[c]	$[PPh_3Au(TA-H)]OTf$ (1%)	CH_3	rt	12	100	43	10	8	35
3[d]	$[PPh_3Au(TA-Me)]OTf$ (1%)	CH_3	rt	12	100	12	16	13	50
4	$[PPh_3Au(TA-Me)]OTf$ (1%)	Ph	rt	12	100	53	trace	trace	trace
5	**$[PPh_3Au(TA-Me)]OTf$ (1%)**	***t*-Bu**	**rt**	**16**	**100**	**<5**	**68**	**12**	**<5**
6	$[(PPh_3Au)_3O]OTf$ (1%)	*t*-Bu	rt	20	100	trace	69	14	<5
7	$[PPh_3Au(TA-Me)]OTf$ (1%) + 2% AgOTf	*t*-Bu	rt	1	100	63	trace	trace	trace
8	$AgSbF_6$ (5%)	*t*-Bu	rt	16	100	45	trace	trace	trace
9	HOTf (5%)	*t*-Bu	rt	16	60	0	0	0	0
10[e]	$PtCl_2$ (5%)	*t*-Bu	80	16	100	0	56	14	<5

[a]Reaction conditions: **1** (0.2 mmol) and catalyst in DCM (0.8 mL), rt, time. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]TA-H = benzotriazole. [d]TA-Me = *N*-methyl benzotriazole. [e]15% yield of (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one.

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the silver catalyst toward alkyne activation (compared with gold catalyst). Triflate acid did not promote the rearrangement at all, giving only the propargyl ester decomposition over time (entry 9). Finally, the silver-free $PtCl_2$ catalyst gave a similar cycloaddition reaction, though at elevated temperature (entry 10). In view of these results, it is clear that the propargyl rearrangement is the initiation step. The reactivity of the three well-known π-acids follows the general trend Au(I) > AgX > $PtCl_2$ in this transformation. Besides alkyne activation, the silver cation (more oxophilic) can also activate the acetate as a leaving group, giving dimer **2** as the only product. The silver-free TA-Au catalyst indicated excellent reactivity toward alkyne activation over the undesired oxygen activation, which led to the successful cycloaddition of allene for the first time. The reaction substrate scope is shown in Figure 2.

The reaction tolerates a good substrate scope on the propargyl aryl position (Ar^1). Electron-withdrawing groups (**3h**, **3k**) were suitable for this reaction, giving the desired

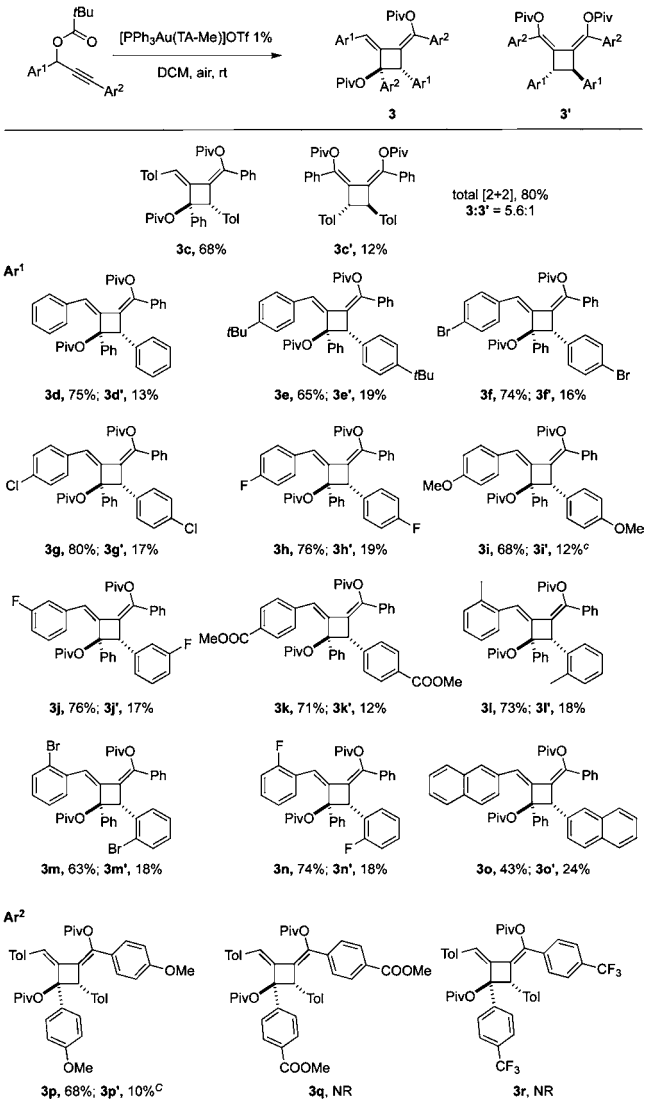

Figure 2. Reaction Scope of [2 + 2] Cycloaddition[a,b] [a] Reaction conditions: **1** (0.2 mmol) and $[PPh_3Au(TA\text{-}Me)]OTf$ in DCM (0.8 mL). [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] 1 mol % of $[(PPh_3Au)_3O]OTf$ was used instead of $[PPh_3Au(TA\text{-}Me)]OTf$.

cycloaddition products in good yields. The electron-donating group modified substrate (**3i**) gave the dimer as one of the major products with TA-Au catalysts, likely due to the improved ability to form a propargyl carbon cation. This problem was overcome by using $[(PPh_3Au)_3O]OTf$ as the catalyst with a longer reaction time. Steric hindrance was not an issue in this transformation considering the fact that *ortho*-substituted substrates (**3l**–**3n**) worked fine under the optimal conditions with the formation of desired [2 + 2] cycloaddition products in excellent yields and similar isomer ratios. Poor selectivity was observed with naphthalene substituted derivative **3o** (1.8:1). This result implied the plausible π–π stacking during the [2 + 2] cycloaddition process.

A greater electronic effect was observed at the alkyne terminal Ar^2 position. The electron-donating *p*-methoxyphenyl substituted alkyne gave the desired cyclobutane **3p** in excellent yield when $[(PPh_3Au)_3O]OTf$ was used as the catalyst. However, an electron-withdrawing group reduced the reaction rate for propargyl ester rearrangement due to either the poor reactivity of alkyne toward π-acid activation (lower electron density) or the unfavored 3,3-migration (over the electronically preferred 1,2-rearrangement). Increasing the reaction temperature to 80 °C (with DCE as solvent) gave the allenes in low yields (<20%), along with a significant amount of unidentified side products. These results suggest that the ambient [2 + 2] cycloaddition is substrate-dependent, which raises the concern whether gold catalysts were involved in the cycloaddition process. To verify the potential role of gold catalysts in the cycloaddition step, we monitored the reaction as shown in Figure 3.

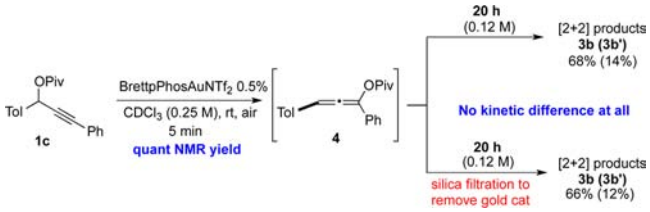

Figure 3. Investigation on the role of Au in [2 + 2] step.

Treating propargyl ester **1c** with silver-free $BrettPhosAuNTf_2$ (0.5%) gave rapid rearrangement (5 min) to allene **4** in quantitative NMR yield. Since allene **4** will decompose upon condensation, it is hard to isolate **4** in pure form. Thus, the reaction mixture was divided into two parts. One part continued to react under the identical conditions (in the presence of the gold catalyst). The other part was filtered through a silica plug to completely remove the gold catalyst. The resulting solvent was condensed to ensure a concentration that was identical to that in the case with the gold catalyst. As reviewed by NMR, for both cases, similar reaction rates were observed, which confirmed that the allene [2 + 2] cycloaddition was a thermal reaction and gold activation was not required.[11]

In conclusion, with the silver-free gold catalyst, the selective [2 + 2] cycloaddition was achieved with high efficiency under mild conditions (rt, open flask). Although the minor isomers were obtained, the fact that only two isolatable cyclobutane isomers were obtained highlighted the good selectivity and high efficiency of this transformation. The silver-free condition was identified as the crucial factor for the success of this transformation. The strong influence of silver salts (even a catalytic amount) raised a viable concern for future

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investigations on gold catalysis, especially when an oxophilic catalyst may be involved.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR data, and crystal data CCDC 992259−992261 (**2a**, **3c**, and **3c**′). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Xiaodong.Shi@mail.wvu.edu.

Notes

The authors declare no competing financial interest.

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