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Gold-Catalyzed Efficient Formation of α,β-Unsaturated Ketones from Propargylic Acetates

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Abstract: An efficient gold-catalyzed method for the preparation of α,β-unsaturated ketones from propargylic acetates has been developed. Under mild reaction conditions, β-monosubstituted enones were formed mostly with excellent *E*-selectivity. β,β-Disubstituted enones can be prepared from propargylic acetates derived from ketones. The high efficiency and mild nature of this reaction render it a viable alternative for the synthesis of α,β-unsaturated ketones.

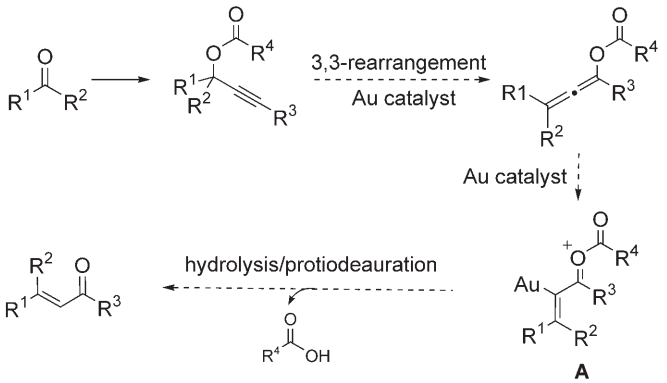
Keywords: catalysis; gold; hydrolysis; ketones; propargylic acetates; rearrangement

α,β-Unsaturated ketones are essential functional groups in organic synthesis. Among various general methods for their preparation, isomerizations of readily accessible propargylic alcohols, i.e., the Meyer–Schuster rearrangement[1] and the Rupe rearrangement,[2] have, however, rather limited usage largely due to narrow substrate scopes and harsh reaction conditions.[3]

Recent discoveries of the exceptional ability of Au catalysts to activate carbon-carbon triple bonds[4] have created new opportunities for developing much milder reactions for the formation of α,β-unsaturated ketones/esters from propargylic precursors.[5] For example, Utimoto[6] reported an efficient transformation of methyl propargyl ethers into α,β-unsaturated ketones using $NaAuCl_4 \cdot 2H_2O$ in refluxing MeOH. Recently, Dudley[7] developed an $AuCl_3$-catalyzed Meyer–Schuster rearrangement of terminally ethoxy-substituted proparyl alcohol, leading to an efficient formation of α,β-unsaturated ethyl esters.

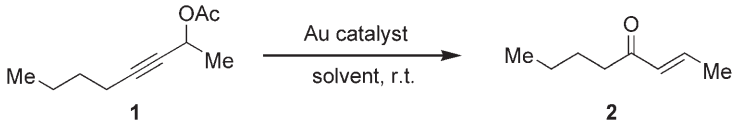
In our continuing effort in developing new synthetic methods *via* Au catalysis,[8] we discovered and herein report an efficient, $Au(PPh_3)NTf_2$-catalyzed synthesis of α,β-unsaturated ketones from propargylic acetates. Notably, besides the ready access to substrates[9] and high efficiency of this reaction, excellent *E*-selectivities were observed in most cases of β-monosubstituted enones.

We have previously shown that propargylic esters derived from aldehydes can be converted into a range of synthetically important products, including alkenyl enol esters/carbonates,[8a] α-ylidene-β-diketones,[8b] cyclopentenones[8c] and highly functionalized 2,3-indoline-fused cyclobutanes[8d] in the presence of gold catalysts. All these transformations can be rationalized by invoking a common, reactive, Au-containing alkenylacyloxocarbenium intermediate (i.e., **A** in Scheme 1), formed *via* tandem Au-catalyzed 3,3-rearrangement of propargylic esters and activation of the *in situ* generated carboxyallenes. Following this line of reasoning, propargylic esters could be converted into α,β-unsaturated ketones *via* hydrolysis/protodeuteration of intermediate **A**, as shown in Scheme 1. While conceptually straightforward, this reaction would be challenging, especially with substrates derived from ketones, as elimination to form enynes can be delete-



Scheme 1. Design of the Au-catalyzed formation of α,β-unsaturated ketones from propargylic esters.

Table 1. Optimization of reaction conditions.[a]



1 2

Entry	Catalyst	Solvent	Time	Conversion [%][b]	Yield [%][b]
1	10 mol % $AuCl_3$	wet CH_2Cl_2	2 h	>99	25
2	10 mol % $(Ph_3P)AuCl/AgSbF_6$	wet CH_2Cl_2	2 h	>99	90
3	2 mol % $(Ph_3P)AuCl/AgSbF_6$	wet CH_2Cl_2	16 h	60[c]	55
4	2 mol % $(Ph_3P)AuCl/AgSbF_6$	2-butanone[d]	16 h	62[c]	55
5	2 mol % $(Ph_3P)AuCl/AgSbF_6$	acetone[d]	16 h	>99	95
6	2 mol % $Au(PPh_3)NTf_2$	wet CH_2Cl_2	16 h	>99	90
7	**2 mol % $Au(PPh_3)NTf_2$**	**2-butanone**[d]	**16 h**	**>99**	**95**[e]
8	2 mol % $Au(PPh_3)NTf_2$	2-butanone/H_2O (160/1)	16 h	>99	95
9	2 mol % $Au(PPh_3)NTf_2$	acetone[d]	16 h	60[c]	55
10	2 mol % $LAuNTf_2$[f]	2-butanone[d]	16 h	>99	95

[a] The concentration of **1** is 0.05 M.
[b] Conversion refers to consumption of propargylic acetate. Yield estimated by ^{1}H NMR using 1,2,3,4-tetramethylbenzene as internal standard.
[c] Catalyst decomposed.
[d] Regular acetone or 2-butanone was used.
[e] 80 % isolated yield in small scales due to the volatility of **2**. In a large scale with 0.5 M of 1 (2-butanone/H_2O = 80 : 1), the reaction finished in 4 h, and **2** was isolated in 90 % yield.
[f] L = 2-(dicyclohexylphosphino)biphenyl.

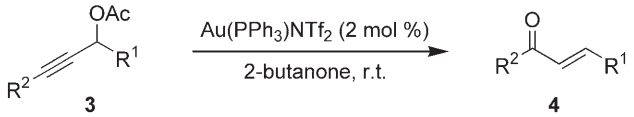
rious and the formation of **A** could be hindered by adverse steric interactions.

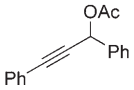
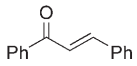
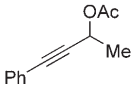
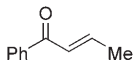
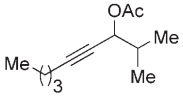
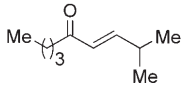
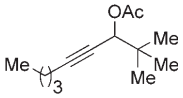
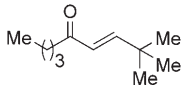
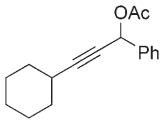
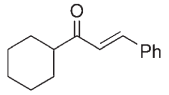
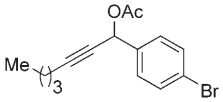
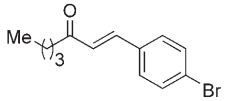
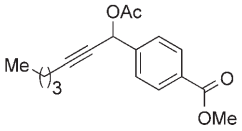
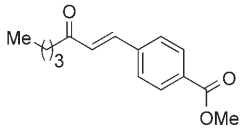
We began with oct-3-yn-2-yl acetate (**1**), readily available from 1-hexyne and acetaldehyde. A range of reaction conditions were tested and some of the results are listed in Table 1. While $AuCl_3$ indeed led to the desired enone **2** albeit in low yield (entry 1), $(Ph_3P)AuCl/AgSbF_6$ catalyzed the formation of **2** efficiently (entry 2), indicating cationic Au(I) complexes to be the preferred catalysts. Noteworthy is the high *E*-selectivity of this reaction, and *Z*-**2** was not observed. In an attempt to lower catalyst loading, we screened different solvents. With 2 mol % of $(Ph_3P)AuCl/AgSbF_6$, the reaction was incomplete even after 16 h due to catalyst decomposition in either wet CH_2Cl_2 or regular 2-butanone. Interestingly, acetone proved to be a suitable solvent, and enone **2** was formed in excellent yield (entry 5). Although a combination of $(Ph_3P)AuCl/AgSbF_6$ and acetone seemed ideal, $[Au(PPh_3)]^+[SbF_6]^-$ was prone to decomposition and had to be prepared *in situ*; moreover, we were concerned that the high reactivity of this catalyst could result in significant elimination in the cases of propargylic acetates dervied from ketones (*vida infra*). Consequently, we chose as catalyst $Au(PPh_3)NTf_2$,[10] which is isolable and less reactive. As shown in entries 6–9, this compound did catalyze the formation of **2**, and regular 2-butanone turned out to be the best solvent (entry 7). The amount of H_2O in 2-butanone was probed, and a mixture of dried 2-butanone and H_2O (160/1) again led to high yield of **2** (entry 8). More elaborate phosphine ligands, such as 2-(dicyclohexylphosphino)biphenyl, also worked well for this reaction (entry 10). We decided to choose the reaction conditions in entry 7 to further study this reaction.

The scope of this chemistry with propargylic acetates derived from aldehydes is shown in Table 2. Various substituents at the propargylic position of acetate **3** were allowed, including aryl groups (entries 1, 5, 6 and 7) and sterically demanding groups (entries 3 and 4). Likewise, the alkyne terminus of **3** can accommodate a range of substituents such as phenyl (entries 1 and 2) and cyclohexyl (entry 5) groups. Good to excellent yields of the desired β-monosubstituted enone **4** were obtained. Moreover, excellent *E*-selectivity was observed in all the studied cases except in entry 5 (E/Z = 8/1). Not surprisingly, acetate **3** with a terminal alkyne (R^1 = Ph and R^2 = H) did not yield enone **4**, and the major product was 1-acetoxy-1-phenylpropan-2-one, formed *via* Au-catalyzed Markovnikov hydration of the carbon-carbon triple bond in 54 % yield.[11]

Expansion of this chemistry to include substrates derived from ketones proved to be challenging as elimination to form enynes and other side reactions became significant. After much effort in optimizing the reaction conditions, we found that 5 mol % of $Au(PPh_3)NTf_2$ (prepared as a 0.05 M solution in ace-

Table 2. Preparation of β-monosubstituted *E*-α,β-unsaturated ketones.



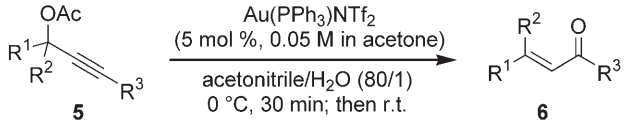
Entry	Propargylic acetate **3**		Time [h]	Enone **4**		Yield [%][a]
1		**3a**	16		**4a**	82
2		**3b**	24		**4b**	78
3		**3c**	16		**4c**	92
4		**3d**	16		**4d**	90
5		**3e**	16		**4e**	88[b]
6		**3f**	12		**4f**	88
7		**3g**	12		**4g**	90

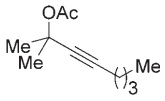
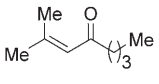
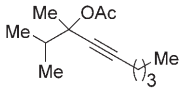
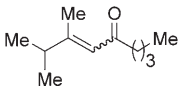
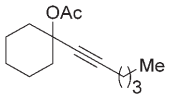
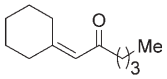
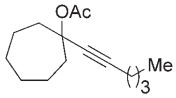
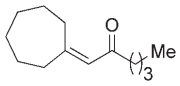
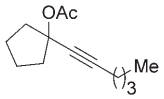
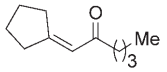
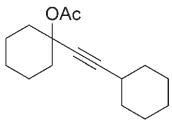
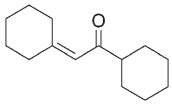
[a] Isolated yield.
[b] An *E*/*Z* (8/1) mixture was formed and isolated.

tone) in acetonitrile/H_2O (80/1) gave rather clean reactions. The use of acetonitrile presumably attenuated the reactivity of $Au(PPh_3)NTf_2$ through solvent coordination as the conditions in Table 2 (2-butanone as solvent) always led to competitive elimination. Interestingly, $Au(PPh_3)NTf_2$ generated as a solution in acetonitrile instead of acetone led to much slower reactions under otherwise identical conditions. Table 3 shows the scope of this reaction using the optimized conditions. Hence, not only was the propargylic acetate **5a** derived from acetone an excellent substrate (entry 1), but also **5b** with more steric hinderance at the propargylic position reacted well under the conditions (entry 2). Compound **5** derived from cyclic ketones such as cyclopentanone (entry 5), cyclohexanone (entry 3), and cycloheptanone (entry 4) underwent similar efficient reactions, leading to the corresponding enones in good to excellent yields. Interestingly, R^3 of compound **5** affects the reaction substantially. Hence, the reaction was efficient with alkyl groups including the sterically demanding cyclohexyl (entry 6), but only 22% of the enone product was isolated when R^3 = Ph and R^1, R^2 = cyclohexyl, and the enal was not formed when R^3 = H and R^1, R^2 = cyclohexyl. Attempts to expand this reaction to include substrates derived from hindered ketones were not successful. For example, in the case of 1-adamantyl methyl ketone, the enone formation was very sluggish, while elimination to form enyne became the predominant process when 2-butanone was used as solvent.

In summary, we have developed an efficient $Au(PPh_3)NTf_2$-catalyzed reaction for the formation of α,β-unsaturated ketones. Under mild reaction conditions, not only propargylic acetates derived from aldehydes but also those from ketones can be converted into α,β-unsaturated ketones in good to excellent yields. Moreover, excellent *E*-selectivity was observed in most cases of β-monosubstituted enones.

Table 3. Preparation of β,β-disubstituted α,β-unsaturated ketones.



Entry	Propargylic acetate **5**		Time [h]	Enone **6**		Yield [%][a]
1		**5a**	16		**6a**	98
2		**5b**	24		**6b**	88[b]
3		**5c**	16		**6c**	97
4		**5d**	16		**6d**	83
5		**5e**	16		**6e**	82
6		**5f**	20		**6f**	93

[a] Isolated yield.
[b] $E/Z = 4/1$.

Experimental Section

General Procedure for the Preparation of β-Monosubstituted α,β-Unsaturated Ketones

To a solution of propargylic acetate derived from an aldehyde (0.2 mmol) in regular 2-butanone (4 mL) was added $Au(PPh_3)NTf_2$ (2.7 mg, 0.004 mmol) at room temperature. The reaction mixture was stirred for the indicated time before being quenched with NEt_3. The reaction mixture was concentrated, and the resulting residue was purified through silica gel flash column chromatography (hexanes/ethyl acetate = 20/1) to yield the desired α,β-unsaturated ketones **4**.

General Procedure for the Preparation of β,β-Disubstituted α,β-Unsaturated Ketones 6

To a solution of propargylic acetate **5** derived from a ketone (0.2 mmol) in anhydrous acetonitrile (4 mL) cooled in ice-water bath were added H_2O (0.05 mL) and $Au(PPh_3)NTf_2$ (0.01 mmol, 0.2 mL of 0.05 M solution in acetone). The reaction mixture was stirred at the same temperature for 0.5 h before warming to room temperature. The reaction was quenched with NEt_3 after being stirred for the indicated time. The reaction mixture was concentrated. The residue was purified through silica gel flash column chromatography (hexanes/ethyl acetate = 20/1) to yield the desired β,β-disubstituted ketones.

Acknowledgements

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