Homogeneous Gold Catalysis | Hot Paper

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Gold(I)-Catalyzed Diastereoselective Hydroacylation of Terminal Alkynes with Glyoxals**

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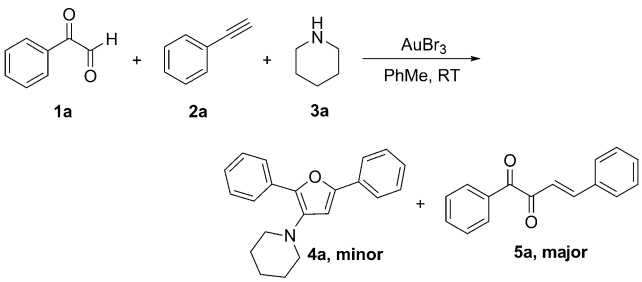
Abstract: *The reaction of an α-ketoaldehyde and a terminal alkyne in the presence of piperidine and a catalytic amount of AuCl delivers 1,2-dicarbonyl-3-enes, products of the formal hydroacylation of the triple bond. The scope of the method is broad; different aryl substituents on the dicarbonyl unit and on the alkyne are well tolerated. The products can be transformed selectively into vinylquinoxalines. Mechanistic studies, including isotope-labeling experiments, indicate that after an initial A^3-type conversion to propargylic amines, a subsequent base-mediated alkyne-to-allene isomerization and a hydrolysis of the enamine substructure during the workup deliver the formal hydroacylation products.*

In the last years, transition-metal-catalyzed Mannich-type three-component coupling reactions of **a**ldehydes, **a**mines and terminal **a**lkynes (A^3 couplings) through C–H bond activation have become an established, convenient, and efficient method for the synthesis of propargylamines.[1] Our group has recently reported an efficient gold-catalyzed oxidation which allowed us to make various glyoxals through the oxidation of terminal alkynes.[2] The application of glyoxals for the construction of organic scaffolds, especially for the generation of heterocycles, is an often used strategy.[3] Since a wide range of aldehydes can be applied in the A^3 coupling, we assumed that glyoxals might also be considered as starting materials, which should open up new applications for this well-known building block. A transformation into different oxopropargyl amines might deliver useful precursors for the synthesis of highly functionalized furans.[4]

To test our hypothesis, we initially attempted to synthesize polysubstituted furans by reacting phenylglyoxal with phenylacetylene and piperidine in the presence of $AuBr_3$. To our surprise, only traces of the expected furan were obtained. Instead, under our reaction conditions the alkenyl-1,2-diketone **5a** with an exclusively *E*-configurated double bond was obtained as the major product, but only in moderate yields (Scheme 1). Encouraged by this unusual result and the fact that alkenyl-1,2-diketones, valuable potential building blocks, are barely documented,[5] we decided to investigate this unexpected transformation in detail.



Scheme 1. Initial observation.

We focused on optimizing the reaction conditions using phenylglyoxal and phenylacetylene as starting materials. Increasing the reaction temperature from room temperature to 50 °C strongly accelerated the reaction rate (Table 1, entry 2). Therefore all of the catalysts were screened at elevated temperatures. Among the employed gold(III) salts, dichloro(2-pyridinecarboxylato)gold[6] (Table 1, entry 6) turned out to be the best catalyst while other complexes containing chloride ligands delivered only poor results. Interestingly, gold(I) chloride gave even better results than the gold(III) salts, while cationic gold(I) sources (activated by a silver(I) salt) delivered poor results (Table 1, entries 8–10). Other transition metals showed low or no conversions (Table 1, entries 11–13); hence we used AuCl for our further optimizations.

As the next optimization step we performed a solvent screening (Table 1, entries 14–20). None of the other solvents was superior to toluene. Polar solvents (Table 1, entries 14 and 15) usually led to faster conversion but lower yields. We further explored the effect of different bases on the reaction (Table 1, entries 21–26). Piperidine gave the best results. Control experiments (Table 1, entries 27 and 28) showed that both a gold catalyst and a base are necessary for this reaction. Attempts to lower the catalyst loadings were unsuccessful and yields dropped significantly (Table 1, entries 29 and 30). In addition, only minor conversion of the starting material resulted when a substoichiometric amount of piperidine was present (Table 1, entry 31). Furthermore, oxygen must be excluded from the reaction system as otherwise α-ketoamides will be produced in quantitative yields (Scheme 2).[7]

Next we explored the scope of this cascade reaction by using glyoxals **1** and terminal alkynes **2** under the optimized

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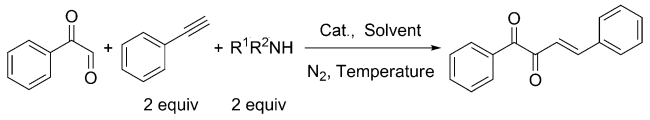
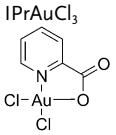
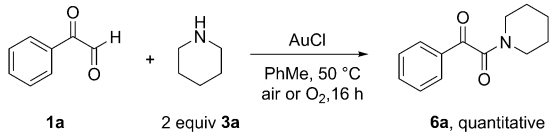
Table 1: Optimization of the catalytic hydroacylation reaction.



Entry	Catalyst[a]	Solvent	R^1R^2NH	T [°C]	t [h]	Yield[b]
1	$AuBr_3$	toluene	piperidine	RT	48	66%
2	$AuBr_3$	toluene	piperidine	50	16	60%
3	$AuCl_3$	toluene	piperidine	50	16	45%
4	$NaAuCl_4 \cdot 2H_2O$	toluene	piperidine	50	16	38%
5	$IPrAuCl_3$	toluene	piperidine	50	16	trace
6		toluene	piperidine	50	16	63%
7	AuCl	toluene	piperidine	50	16	71%
8	Ph_3PAuCl/$AgNTf_2$	toluene	piperidine	50	16	trace
9	IPrAuCl/$AgNTf_2$	toluene	piperidine	50	16	trace
10	$AuBr_3$/3 AgOTf	toluene	piperidine	50	16	trace
11	AgOTf	toluene	piperidine	50	16	trace
12	CuCl	toluene	piperidine	50	16	19%
13	$PtCl_2$	toluene	piperidine	50	16	trace
14	AuCl	$CHCl_3$	piperidine	50	3	34%
15	AuCl	CH_3CN	piperidine	50	5	15%
16	AuCl	CH_2Cl_2	piperidine	50	16	47%
17	AuCl	THF	piperidine	50	16	53%
18	AuCl	benzene	piperidine	50	16	55%
19	AuCl	hexane	piperidine	50	16	trace
20	AuCl	Et_2O	piperidine	50	16	trace
21	AuCl	toluene	Et_2NH	50	18	16%
22	AuCl	toluene	Et_3N	50	18	NR
23	AuCl	toluene	morpholine	50	16	32%
24	AuCl	toluene	pyrrolidine	50	16	41%
25	AuCl	toluene	$(nBu)_2NH$	50	16	25%
26	AuCl	toluene	hexamethyleneimine	50	16	42%
27	–	toluene	piperidine	50	16	NR
28	AuCl	toluene	–	50	16	NR
29	AuCl[c]	toluene	piperidine	50	16	44%
30	AuCl[d]	toluene	piperidine	50	16	31%
31	AuCl	toluene	piperidine[e]	50	16	trace

[a] 10 mol% catalyst. [b] Yield of isolated product. [c] 3 mol% catalyst. [d] 1 mol% catalyst. [e] 0.2 equiv piperidine. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = triflate, NR = no reaction.



Scheme 2. Gold-catalyzed oxidative coupling of phenylglyoxal and piperidine.

conditions (2.0 equiv of piperidine, 10 mol% AuCl, toluene, N_2 atmosphere, 50°C). The results are summarized in Scheme 3. A wide range of alkenyl diketones could readily be obtained by following this procedure. The reactions of phenylglyoxal **1a** with various terminal alkynes were first examined. Phenylacetylenes bearing either electron-donating or electron-withdrawing groups afforded the corresponding products in good to moderate yields (**5b–j**). However, **5k** was obtained in only 29% yield most probably due to the strong electron-withdrawing effect of the nitro group. Biphenyl, naphthyl, and thiophenyl moieties were also tolerated in this reaction (**5l–n**). Attempts to prepare bis-hydroacylated products in a bidirectional process failed. Instead, only mono-hydroacylation products were obtained in moderate yields (**5o**,**p**). In addition to the aromatic systems, an aliphatic alkyne could also be transformed (**5q**), albeit in low yields. Finally, two other glyoxal derivatives were tested. Both of them turned out to be suitable starting materials leading to the desired products in moderate yields (**5r**,**s**). Most of these reactions had a clear preference for the *E* diastereomer; an olefinic coupling constant of 16.2–16.4 Hz clearly demonstrated that. Only in a few cases were small amounts (7.5–10%) of the *Z* product detected.

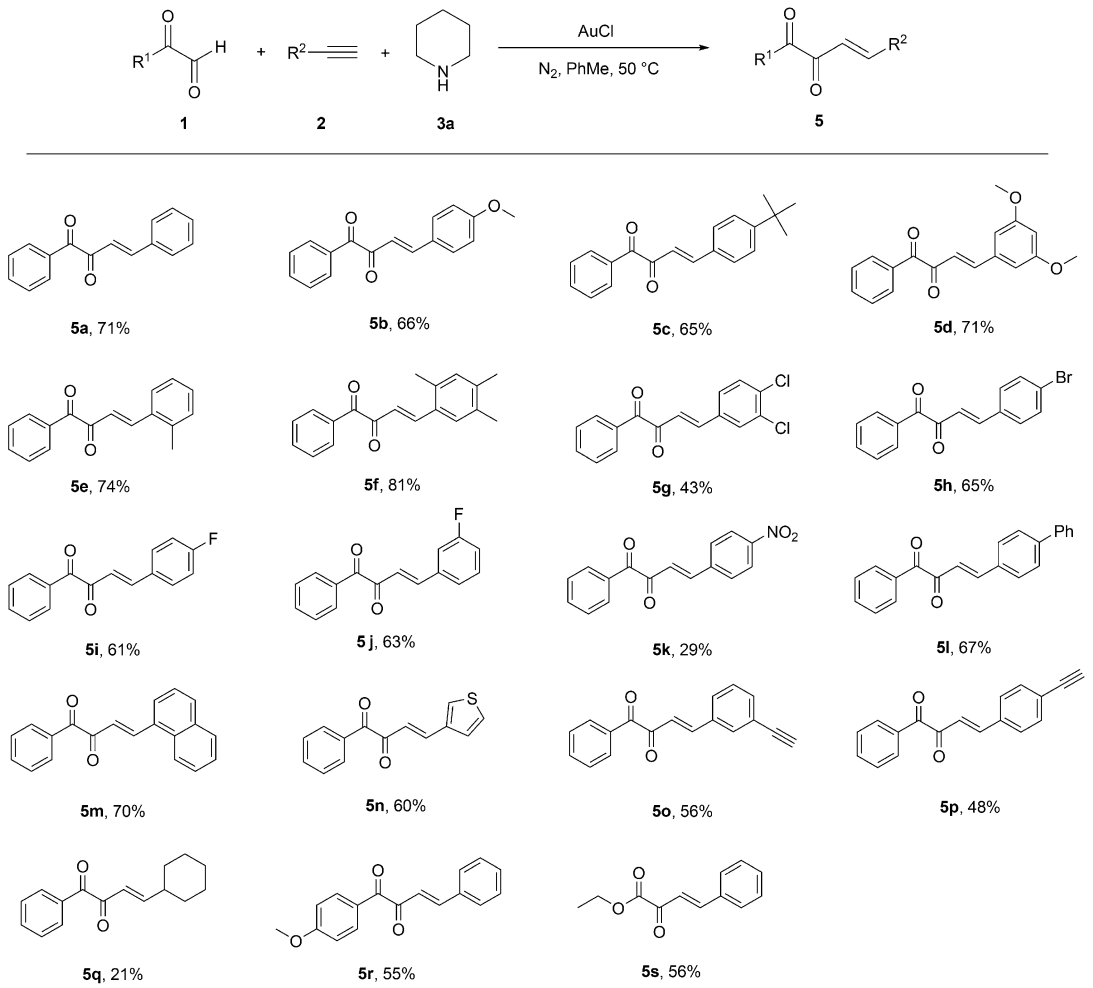
The products prepared by this procedure are valuable precursors for the synthesis of heterocycles. For example, **5a** could readily be reacted with *o*-phenylenediamine to afford the interesting vinyl-substituted quinoxaline **6a** in good yield (Scheme 4).

As the next step we investigated the reaction mechanism. When the crude product was directly analyzed by ^1H NMR spectroscopy, surprisingly, product **5a** was not detected. Only the spectrum of a complex mixture was obtained. GC/MS analysis showed that the mixture contained one main product with a molecular weight corresponding to the A^3 coupling product **7a**. The final product **5a** became the main component after silica gel was added to this crude product (Scheme 5).

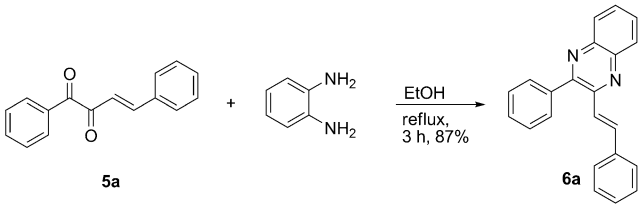
To gain further insight, the α-deuterated phenylglyoxal was prepared by oxidation of deuterated phenylacetylene.[2] Its conversion under standard conditions showed no deuterium incorporation into the final product, which excludes a 1,3-hydrogen shift[8] as an elementary step of the reaction mechanism. Our next labeling experiment was conducted with D_2O as a deuterium source and product **5a′** was obtained. Both of the double-bond positions bear deuterium labels (46% and 63% incorporation). In another labeling experiment, the crude intermediate, which was obtained directly by evaporating toluene from the reaction mixture, was added to an acetone/$H_2{}^{18}O$ mixture which resulted in the ^{18}O-labeled product **5a″**. [D_{11}]Piperidine was then used as a base but no deuterium was incorporated into product **5a**, which excludes a possible 1,5-hydride shift from the piperidine onto the activated alkyne[9] (Scheme 6).

On the basis of these observations we propose the following mechanism (Scheme 7): Initial gold-catalyzed A^3 coupling results in carbonyl propargylamine **6a**. Based on the acceptor in α-position (which is not present in the known A^3 couplings), the acidity of the propargylic proton is enhanced which enables isomerization[10] (assisted by the piperidine) to give the conjugated allenylamine intermediate **6a′**. Hydrolysis of the enamine substructure on silica gel then leads to the final product **5a**; the thermodynamically more stable *E* diastereomer is formed preferentially.

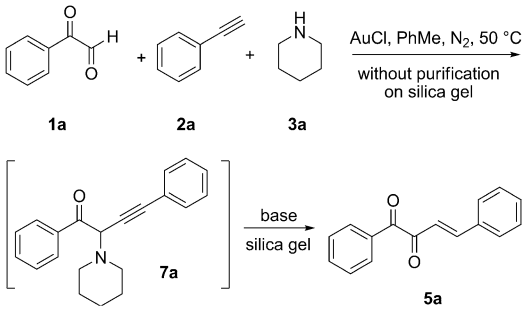
In conclusion, we have developed an efficient cascade reaction for the preparation of alkenyl-1,2-diketones from



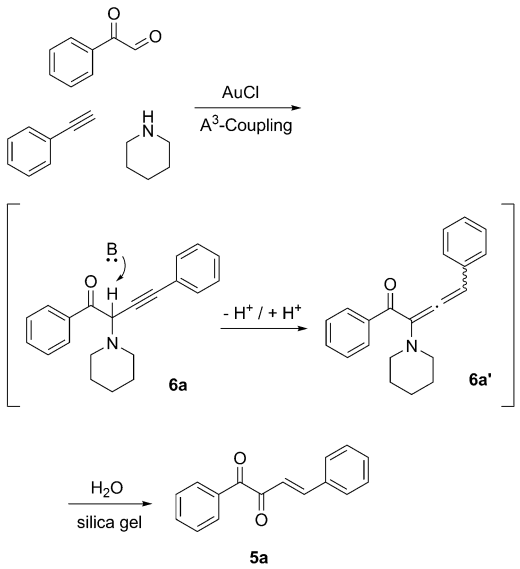
Scheme 3. Synthesis of alkenyl 1,2-diketones from different glyoxals and alkynes. Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), piperidine (**3a**, 0.6 mmol), AuCl (7 mg, 10 mol%), toluene, N_2 atmosphere, 50°C, yield of isolated product.



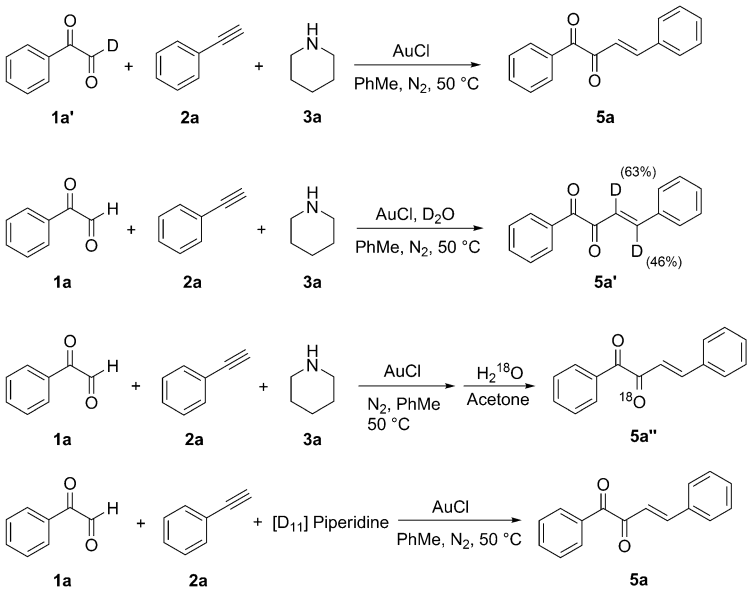
Scheme 4. Synthesis of vinylquinoxaline derivative **6a** from **5a**.



Scheme 5. Conversion of intermediate **7a** into the final product.



Scheme 7. Reaction mechanism in accordance with the labeling studies.



Scheme 6. Labeling experiments.

readily available staring materials. The obtained alkenyl-1,2-diketones can serve as useful building blocks for the synthesis of heterocycles, which was demonstrated by the formation of a vinylquinoxaline derivative. Further research on the scope and mechanism of this new gold-catalyzed hydroacylation is ongoing in our laboratories.

Experimental Section

An N_2-protected Schlenk tube was charged with anhydrous toluene (2 mL), glyoxal derivative **1** (0.3 mmol, 1.0 equiv), alkyne **2** (0.6 mmol, 2.0 equiv), piperidine **3a** (0.6 mmol, 2.0 equiv), and AuCl (7 mg, 0.1 equiv) in sequence. This solution was stirred at 50 °C for 16 h under an N_2 atmosphere. After complete conversion, as monitored by TLC analysis, the solvent was evaporated and the residue was purified by column chromatography on silica gel.

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