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Highly Efficient Gold(I)-Catalyzed Regio- and Stereoselective Hydrocarboxylation of Internal Alkynes.

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ABSTRACT: We report the highly efficient gold-catalyzed hydrocarboxylation of internal alkynes that operates under solvent- and silver-free conditions. This new simple and eco-friendly protocol allows for the synthesis of a wide variety of functionalized aryl and alkyl enol esters in high yields, with *Z*-stereospecificity, good regioselectivities and without the requirement for purification by chromatography. This process represents an expedient, operationally simple method for the synthesis of enol esters.

Enol esters are highly versatile building blocks in organic synthesis.[1] They are widely used industrially in polymerization processes[2] and have also been shown to be valuable reagents in a variety of synthetic transformations.[3] Among a wide variety of synthetic approaches previously developed, the direct addition of widely available and inexpensive carboxylic acids starting materials to alkynes represents the most efficient route to access vinyl esters due to excellent atom- and step-economies.[4] While the intermolecular addition of carboxylic acids to terminal alkynes has been extensively studied,[5] the use of unactivated internal alkynes has been shown to be particularly difficult and requires high catalyst loadings, long reaction times and increased temperatures.[6] Additionally, further challenges remain in developing the next generation of such reactions, namely the regio-, stereo- and chemoselectivity (Markovnikov and anti-Markovnikov products) of these reactions. Furthermore achieving this in a manner where products can be accessed efficiently, with minimal waste and purification would be quite an achievement. There is a clear need for new methods to overcome these challenges and limitations.

With its high affinity for π-systems, gold has been shown to be uniquely effective in the addition of nucleophiles to unsaturated systems such as alkynes or allenes.[7] While numerous reports describe the cyclization of alkynoic acids to give γ-lactones,[8] examples of the intermolecular addition of carboxylic acids to alkynes catalyzed by gold remain few. So far, only two reports using Au(I) can be found in the literature. In 2010, Chary *et al*. reported the hydrocarboxylation of alkynes using 5 mol% of $[Au(PPh_3)Cl]/AgPF_6$.[5j] This methodology was applied to various terminal alkynes but was only demonstrated with four internal alkynes. In particular, incomplete conversion and lower yield were observed when using unreactive diaryl-substituted alkynes. A recent report by Zhang and co-workers described a strategy using a tailored phosphine ligand to direct and promote the nucleophilic addition to gold-activated alkynes.[5k] The addition of benzoic acid to three internal aliphatic alkynes was examined and proceeded smoothly using low loadings of [Au] but required long reaction times (12-24 h).

To the best of our knowledge, no report of a highly efficient and broadly applicable hydrocarboxylation of internal alkynes using gold and especially (NHC)Au catalyst systems has been disclosed to date. Our group recently demonstrated that $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ (**1a**) is a highly efficient bifunctional catalyst for the hydrophenoxylation of internal alkynes.[9] Notably, this complex can be regarded as a dual-mode activating catalyst providing Lewis acid $[Au(IPr)][BF_4]$ (**1b**) and Brønsted base [Au(IPr)(OH)] (**1c**) fragments (eq. 1).[9b]

$$[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4] \rightleftharpoons [Au(IPr)][BF_4] + [Au(IPr)(OH)] \quad (1)$$

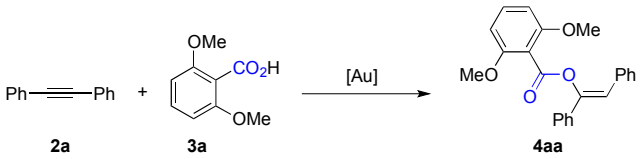
1a **1b** **Lewis acid** **1c** **Brønsted base**

We envisioned that this strategy could also be applied successfully to accomplish other challenging reactions such as the intermolecular addition of carboxylic acids to internal alkynes to produce a broad variety of functionalized enol esters with hopefully excellent regio- and stereoselectivity.

Initially, diphenylacetylene (**2a**) and the sterically hindered 2,6-dimethoxybenzoic acid (**3a**) were selected as model substrates. To our delight, the addition of **3a** to **2a** (1.1. equiv.), at 85 °C in technical-grade toluene (1M) in the presence of 2 mol% of $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ **1a** gave complete conversion to vinyl ester (**4aa**) as a single stereoisomer, after 16 h (Table 1, entry 1). The ^{1}H NMR of the reaction mixture confirmed the stereospecific formation of (*Z*)-isomer. Subsequently, various gold catalysts were examined. Interestingly, the Brønsted base [Au(IPr)(OH)] **1c** gave only 40% conversion while cationic Gagosz complex $[Au(IPr)(NTf_2)]$[10] **1f** alone failed to catalyze the hydrocarboxylation of **2a** (Table 1, entries 3-4). High conversion was obtained using $[Au(IPr)(MeCN)][BF_4]$ **1e** catalyst, albeit longer reaction time was required and the desired vinyl ester was formed along with 15% of ketone side-product due to the competing hydration of **2a** (Table 1, entry 5).[9c] Complex **1e** is known to form

digold hydroxide **1a** in the presence of water.[9b] These results gave us confidence that a bifunctional catalyst enhanced reactivity. The solvent was found to also have an important

Table 1. Reaction Development of the Au(I)-Catalyzed Addition of Carboxylic Acids to Alkynes[a]



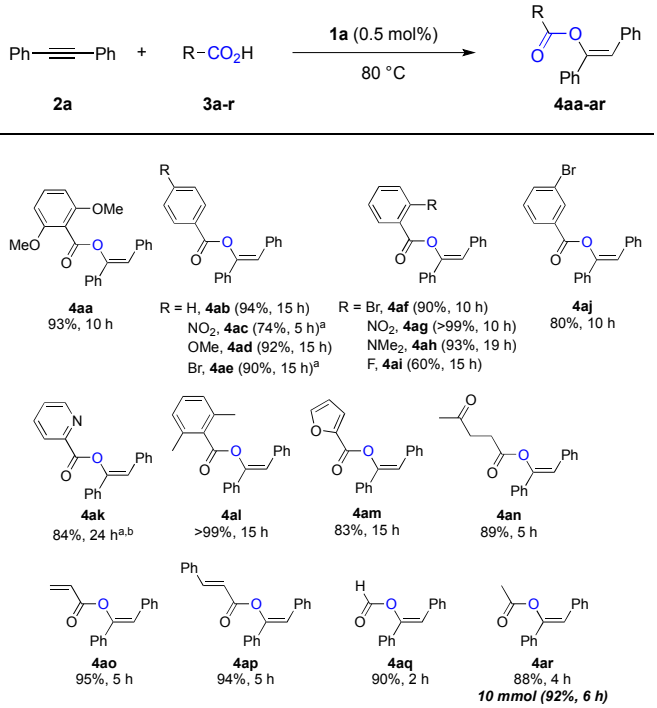
Entry	Catalyst	Solvent	Conversion (%)[b]
1	[{Au(IPr)}$_2$(μ-OH)] (**1a**) (2 mol%)	Toluene	>99[c,d]
2	[{Au(SIPr)}$_2$(μ-OH)] (**1d**) (2 mol%)	Toluene	34[c,d]
3	[Au(IPr)(OH)] (**1c**) (4 mol%)	Toluene	40[c,d]
4	[Au(IPr)(MeCN)][BF_4] (**1e**) (4 mol%)	Toluene	70[c,d]
5	[Au(IPr)(NTf_2)] (**1f**) (4 mol%)	Toluene	0[c,d]
6	**1a** (0.5 mol%)	Toluene	65
7	**1a** (0.5 mol%)	Neat	>99 (93%)
8	**1c** (0.5 mol%) + **1e** (0.5 mol%)	Neat	93%

[a]Conditions: alkyne (0.5 mmol), carboxylic acid (0.5 mmol), solvent (1 M), 80 °C, 16 h. [b]Conversion determined by GC. [c]**2a**/**3a** (1.1/1). [d]85 °C.

influence on the course of the reaction with toluene being optimal (see ESI for further optimization studies). Slower reaction rate was observed with a 1/1 ratio of **2a**/**3a** and a further decrease of the catalyst loading to 0.5 mol% (Table 1, entry 6). To reduce the environmental impact of the process, the reaction was carried out under solvent-free conditions. Gratifyingly, using 0.5 mol% of **1a**, 74% conversion was observed after 5 h and the reaction was complete after 10 h affording (*Z*)-vinyl ester **4aa** in 93% yield without traces of hydration side-product (Table 1, entry 7). As previously mentioned, digold hydroxide **1a** can be seen as the combination of [Au(IPr)(OH)] **1c** and [Au(IPr)][BF_4] **1b**. Since complex **1b** is not a stable species, **1e** is generally used as a substitute. We were pleased to see that using 0.5 mol% of both **1c** and **1e** led to high conversion to vinyl ester **4aa** (93%) as well (Table 1, entry 8). This result strongly supports that **1a** acts as a bifunctional catalyst for the hydrocarboxylation of alkynes. Remarkably, these conditions allow for a very simple and economical work-up procedure; pentane is simply added to the crude mixture and the pure vinyl esters can be isolated by filtration *without the need for chromatography or any further purification*. Precautions to exclude air are unecessary in this procedure.

With the optimized conditions in hand, the scope of the reaction was initially explored using diphenylacetylene **2a** and a wide variety of carboxylic acids (Scheme 1). The methodology proved to be broadly applicable and a diverse range of vinyl esters could be synthesized with complete stereoselectivity. Therefore, a series of functionalized (*Z*)-diphenylvinyl benzoates could be obtained in good to excellent yields (60-99% yield). The nature of the substituent on the aryl ring of the benzoic acids had little influence on the reaction yield and a variety of electron-donating and withdrawing substituents could be tolerated including bromo (**3e**, **3f** and **3j**), nitro (**3c** and **3g**), methoxy (**3a** and **3d**), fluoro (**3i**) and even substituted amine (**3h**) groups. The use of sterically hindered benzoic acids did not affect the reaction rate and led to compounds **4aa** and **4al** in high yields.

Scheme 1. Hydrocarboxylation of diphenylacteylene 2a with aryl and alkylcarboxylic acids



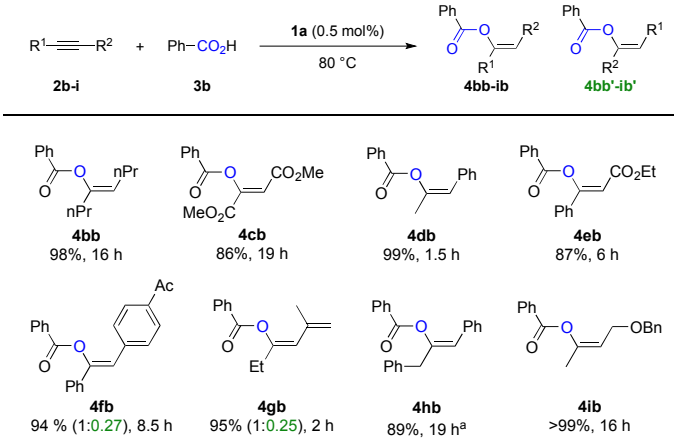
Reaction Conditions: Alkyne (0.5 mmol), carboxylic acid (0.5 mmol), [Au] (0.0025 mmol), 80 °C. Isolated yields. Average of two runs. [a]110 °C. [b]Using 1 mol% of **1a**.

Pleasingly, the addition of heteroarylcarboxylic acids such as 2-picolinic acid (**3k**) and furoic acid (**3m**) proceeded smoothly without affecting the catalyst activity. Furthermore, this methodology was also applicable to vinylcarboxylic acids such as acrylic acid (**3o**) and cinnamic acid (**3p**) providing access to compounds **4ao** and **4ap**, in short reaction times and with excellent yields and complete chemoselectivity. This reactivity is remarkable as acrylic acid is well-known to undergo very facile polymerization. Gratifyingly, the methodology could be extended to several aliphatic carboxylic acids. The reactions with these substrates proceeded much faster, most likely due to their enhanced nucleophilicity, and without any loss of stereoselectivity, forming the product (*Z*)-isomer only. Both formic acid (**3q**) and acetic acid (**3r**) were also successfully converted in high yields to the corresponding vinyl esters. It is worth mentioning that, to date, vinyl acetate has only been obtained in a maximum of 62% yield using alternative methodologies.[5j] Also, the particular stability of vinyl acetate, under these conditions, is remarkable as this compound easily polymerize to polyvinyl acetate - one of the industrially most important homopolymer.[11] Finally, a reaction was conducted on a 10 mmol-scale (1.78 g of **2a**), a 92% yield

(2.19 g) of (*Z*)-1,2-diphenylvinylacetate **4ar** could be successfully isolated after simple filtration.

Encouraged by these results, the reactivity of both symmetrical and unsymmetrical alkynes with benzoic acid (**3b**) was next examined (Scheme 2). Interestingly, the reactions were found to be faster with unsymmetrical than symmetrical alkyne substrates. In general, good to complete regioselectivities were observed using unsymmetrical alkynes with the addition of benzoic acid **3b** occurring at the most electrophilic carbon of the triple bond.

Scheme 2. Addition of benzoic acid to unsymmetrical internal alkynes



Reaction Conditions: Alkyne (0.5 mmol), carboxylic acid (0.5 mmol), [Au] (0.0025 mmol), 80 °C. Isolated yields. Average of two runs. Ratio determined by ^{1}H NMR. [a]Using 1 mol% of **1a**.

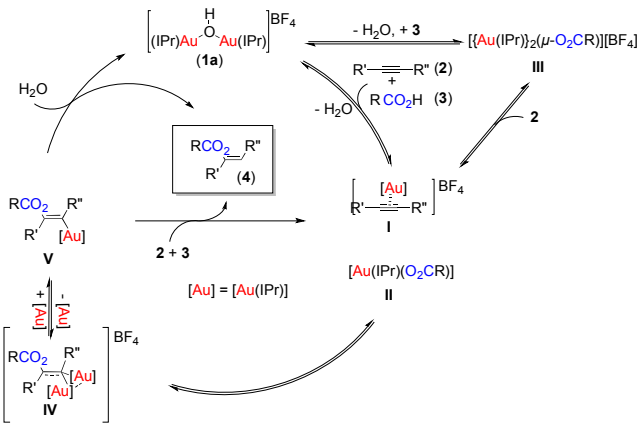
Under our previous conditions, both 4-octyne (**2b**) and dimethylacetyldicarboxylate (DMAD) (**2c**) were successfully converted, again with complete stereoselectivity, to vinyl ester (**4bb**) and dimethyl fumarate (**4cb**) in high yields. Remarkably, the reactions of both phenylpropyne (**2c**) and phenylpropiolate (**2d**) afforded the vinyl esters (**4db**) and (**4eb**) in complete regio- and stereoselectivity. Diaryl-substituted alkyne **2f** underwent hydrocarboxylation with good regioselectivity. Similarly, good regio- and complete chemoselectivity was obtained when reacting enyne **2g**. Finally, total conversion of unsymmetrical alkynes **4h** and **4i** into vinyl esters **4hb** and **4ib** was achieved with complete regio- and stereoselectivity.

Next, the recyclability of the catalyst was assessed. Formic acid **4q** and diphenylacetylene **2a** substrates were chosen as the test reaction for sake of expediency. Once the reaction was complete, iterative additions of both substrates were performed. As a result, 6.5 mmol of **2a** was converted to **4aq** using 2.5 µmol of **1a**, affording an exceptional turnover number (TON) of 2610 for this reaction (compared to a TON of 18 reported in ref 5j). This attests to the robustness of the catalytic system as once again no precaution to exclude air and moisture was taken.

On the basis of previous mechanistic studies,[9b] the following mechanism can be proposed for the gold(I)-catalyzed hydrocarboxylation of alkynes (Scheme 3).

Two initiation steps can be envisaged. In a dual activation mode, **1a** would dissociate into Lewis acid [Au(IPr)][BF_4] **1b** and Brønsted base [Au(IPr)(OH)] **1c**. The former would coordinate to the alkyne **2** to form π-gold-alkyne complex **I**,[12] while the latter would deprotonate the carboxylic acid **3** to generate gold carboxylate **II**.[13] In a parallel scenario, digold hydroxide **1a** could directly react with carboxylic acid **3** to

Scheme 3. Proposed mechanism



form digold carboxylate **III**. This species, in the presence of alkyne **2**, would be in equilibrium with **I** and **II**. From this point, subsequent nucleophilic attack of gold carboxylate **II** toward π-complex **I** in an *anti*-fashion would lead to the formation of *gem*-diaurated species **IV**[14] or σ-monoaurated species **V**,[15] most likely in equilibrium – the former being rather an off-cycle species.[14b]Finally protodeauration with either H_2O or carboxylic acid would deliver the final vinyl ester **4**. This represents the possibilities enabling the transformation. Efforts aimed at clarifying the exact mechanistic route leading to product are presently being carried out in our laboratory.

In summary, we have developed a straightforward and highly efficient methodology for the hydrocarboxylation of internal alkynes catalyzed by a digold hydroxide complex enabling the formation of various aryl and alkyl vinylesters in good to excellent yields with superb regio-, chemo- and stereoselectivity. In addition, the use of solvent-free conditions not only permits a practical, operationally simple and scalable strategy but leads to faster reaction kinetics. The present process represents a practical and atom-economical alternative to existing synthetic methods to assemble vinyl ester motifs that are not easily accessed. Further studies aimed at extending the reaction scope and at exploring the potential use of **1a** in other transformations are currently underway.

ASSOCIATED CONTENT

Supporting Information. Optimization studies, experimental procédures, characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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