Letter

Chlorine-Tolerant Gold(I) Catalyzed Regioselective Hydrochlorination of Alkynes

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Chloride-Tolerant Gold(I) Catalyzed Regioselective Hydrochlorination of Alkynes

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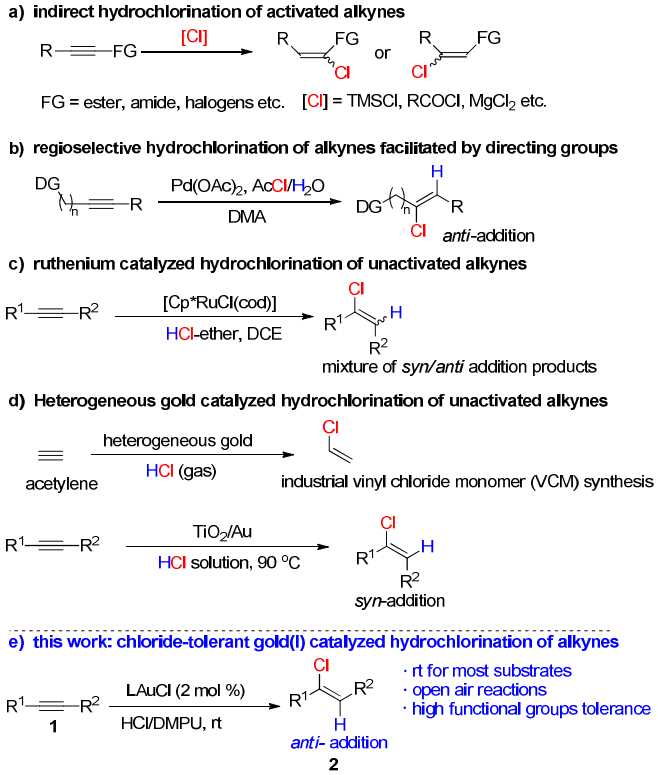
Supporting Information Placeholder

ABSTRACT: We have developed a highly regioselective homogeneous gold(I)-catalyzed *anti*-hydrochlorination of unactivated alkynes at room temperature. We have overcome the incompatibility between conventional cationic gold catalysts and chloride by using a hydrogen bonding activation of Au-Cl bond. This approach is scalable, exhibits excellent functional group tolerance, and can be conducted in open air.

KEYWORDS: gold catalysis, hydrochlorination, chloride-tolerant, alkyne, HCl/DMPU

Chlorination is one of the most important transformations in organic synthesis because of the biological activities and synthetic value of the chlorinated products.[1] More specifically, vinylchloride is one of the most important group of chlorine-containing compounds. Vinylchlorides are widely found in natural products, pharmaceuticals and agrochemicals,[1-2] and also are valuable coupling partners in coupling reactions such as Buchwald-Hartwig amination[3] and Suzuki-Miyaura coupling.[4] Compared to the traditional syntheses of vinylchlorides, such as halogenations of carbonyl compounds[5] and electrophilic chlorination of alkynes,[6] the direct hydrochlorination of alkynes from HCl is a straightforward and atom-economic method. However, given that HCl itself is a dangerous gas and handling is problematic, synthetic chemists have focused on indirect hydrochlorination strategies for activated alkynes,[7] using RCOCl, TMSCl or metal chlorides as chlorine sources (Scheme 1a).[8] One notable example is the recent work by Engle and coworkers on the palladium-catalyzed *anti*-hydrochlorination of alkynes using a directing group (Scheme 1b).[9] The direct hydrochlorination of unactivated alkynes using HCl has been rarely reported. Dai and coworkers found that gaseous HCl could hydrochlorinate electron-rich phenylacetylenes but the use of gaseous HCl, and hydration side products present major drawbacks.[10] Derien and coworkers developed a ruthenium-catalyzed hydrochlorination of alkynes that gave good yields (Scheme 1c).[11] Although this method works well for terminal alkynes, higher temperature was needed and low stereoselectivity was observed for internal alkynes (Scheme 1c). Moreover, a restrictive Schlenk environment was essential. The heterogeneous gold catalyzed hydrochlorination of acetylene for manufacture of vinyl chloride monomer (VCM) is a well-studied process,[12] and has been industrialized recently (Scheme 1d).[13] Recently, and independently, Corma group[14] and our group[15] reported a heterogeneous gold (TiO_2/Au) catalyzed hydrochlorination reaction of alkynes. Although good *syn*-addition selectivity was observed, high temperatures were needed (Scheme 1d).

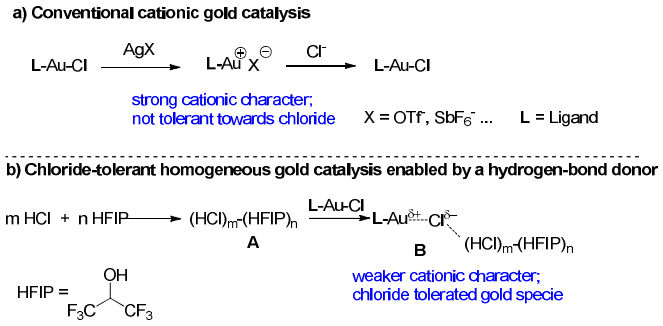


Scheme 1. Major synthetic methods for chlorination of alkynes to synthesize vinylchlorides.

Although homogeneous cationic gold catalysts are considered as the most powerful catalysts for the electrophilic activation of alkynes,[16] the cationic gold-catalyzed hydrochlorination of alkynes has not been reported because of the high affinity between cationic gold and chloride.[17] Indeed, commonly used gold pre-catalysts, such as PPh_3AuCl, usually need silver salts to break the strong Au-Cl bond and release an active cationic gold species and chloride is known to easily poison cationic gold species (Scheme 2a).[18] We are now pleased to report a

homogenous gold-catalyzed alkyne hydrochlorination with exclusive *anti*-selectivity that overcomes the incompatibility between cationic gold catalysts and chloride (Scheme 1e).

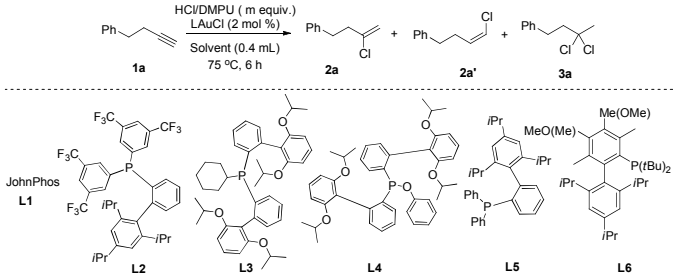
We proposed that a combination of strong hydrogen bond donor solvents such as hexafluoroisopropanol (HFIP), and HCl would generate a strong hydrogen bonding donor network **A**, and that the hydrogen bonding between chlorine in L-Au-Cl and **A** might weaken the Au-Cl bond (Scheme 2b). This would generate a partially cationic gold species **B** *via* hydrogen bonding interaction. This strategy would avoid the use of a silver salt to activate the gold pre-catalyst, a step that is known to exert negative effects in gold catalysis.[19]



Scheme 2. Conventional cationic gold catalysis and chloride-tolerant homogenous gold catalysis.

We used 4-phenylbutyne **1a** as the model substrate for reaction optimization. We screened various ligands, HCl sources and solvents (Table 1).

Table 1. Screening of homogeneous gold catalyzed hydrochlorination of alkynes.



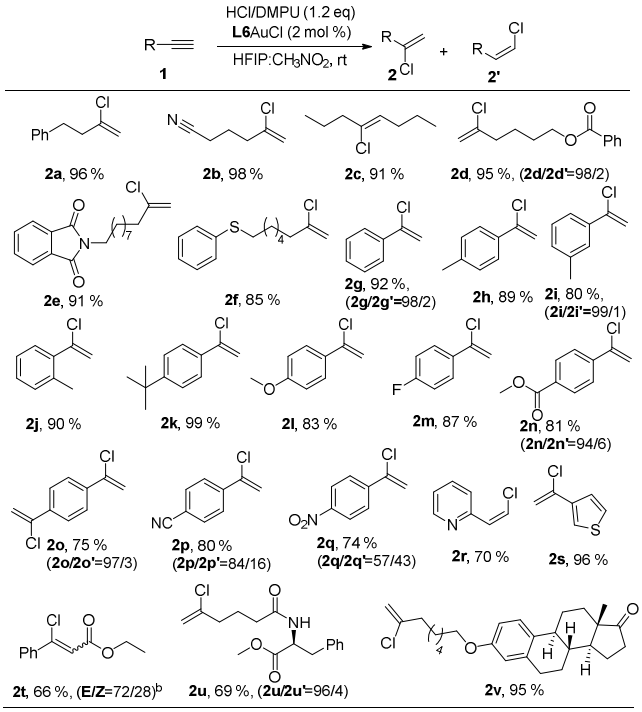
Entry	L	m	HCl	Solvent	Yield (%)[a]	Ratio of **2a**:**2a'**:**3a**
1	L1	1.5	HCl/DMPU	HFIP	80	75:8:17
2	L2	1.5	HCl/DMPU	HFIP	55	76:9:15
3	L3	1.5	HCl/DMPU	HFIP	65	90:8:2
4	L4	1.5	HCl/DMPU	HFIP	38	82:9:9
5	L5	1.5	HCl/DMPU	HFIP	95	93:4:3
6	L6	1.5	HCl/DMPU	HFIP	96	90:7:3
7	L5	1.2	HCl/DMPU	HFIP	95	95:4:1
8[b]	L5	1.2	HCl/DMPU	HFIP	98	97:3: -
9[b]	L6	1.2	HCl/DMPU	HFIP	95	97:3: -
10	-	2.4	HCl/DMPU	HFIP	34	59:16:25
11[b]	L5	1.2	HCl/*i*PrOH	HFIP	72	88:12: -
12[b]	L5	1.2	HCl/Et_2O	HFIP	<5	n. a.
13[b, c]	L6	1.2	HCl/DMPU	*t*BuOH	85	51: -: -
14[b, c]	L6	1.2	HCl/DMPU	THF	78	82:8: -
15[b, d]	L6	1.2	HCl/DMPU	HFIP/$MeNO_2$	97	99:1: -
16[b, d]	L6	1.2	HCl/DMPU	HFIP/ DMF	93	98:2: -

[a]Yields were determined by GC-MS using dodecane as internal standard. [b]Reaction run at rt for 24 h. [c]Ketone product formed (accounts for the remaining ratio of product). [d]Solvent mixture is 1:1 by volume.

Due to its high hydrogen bond basicity but low Brønsted basicity,[20,21] DMPU is able to form a stable and highly concentrated complex with hydrogen chloride (HCl).[15] Using 1.5 equiv of HCl/DMPU and 2 mol % of gold catalyst and various ligands (**L1**-**L6**) led to high yields of product (Table 1, entries 1-6). However, the *anti*-Markovnikov and dichlorinated products were also obtained in varying amounts. The use of **L5** improved the selectivity of the produced vinylchloride to 95 % yield, needing only 1.2 equiv of HCl/DMPU (Table 1, entry 7). Formation of the dichlorinated byproduct was avoided by running the reaction at ambient temperature (Table 1, entry 8-9), with both **L5** and **L6** working equally well. A poor yield was obtained in the absence of gold (Table 1, entry 10). Notably, lower selectivity and poor yields were observed when commercially available HCl sources (HCl/*i*PrOH and HCl/ether) were used (Table 1, entries 11 and 12). We screened other solvents to further optimize the regioselectivity. We found that a 1:1 HFIP: CH_3NO_2 mixture provided optimal conditions. It is worth noting that *tert*-butanol and THF gave substantial amounts to the corresponding ketone. A 1:1 HFIP: DMF combination worked well also (Table 1, entry 16).

With optimized conditions in hand, we investigated the substrate scope (Table 2). We first examined the scope of aliphatic alkynes. A wide variety of terminal alkynes reacted smoothly to give the corresponding vinylchlorides in good to excellent yields.

Table 2. Substrate scope of homogeneous gold catalyzed hydrochlorination of alkynes.[a]



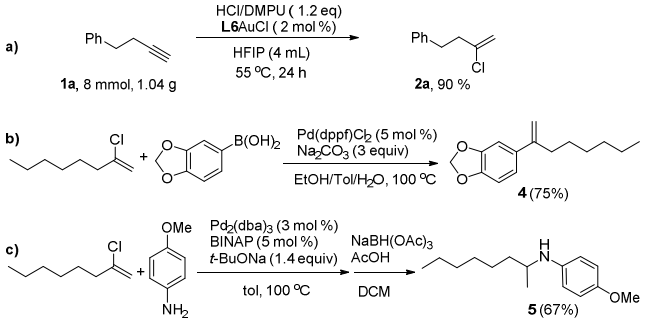
[a]Reaction conditions: alkyne **1** (0.5 mmol), HCl/DMPU (1.2 equiv), **L6**AuCl (2 mol %), HFIP:CH_3NO_2 (0.125 mL) at rt for 16-36 h. Isolated yields. [b]75 °C was used.

Nitrile (**2b**), ester (**2d**), imide (**2e**), sulfide (**2f**), amide (**2u**), and ketone ether (**2v**) functional groups were well tolerated under the standard conditions. The reaction with derivatized amino acid (**2u**) and the natural product estrone (**2v**) led toteh corresponding products in 69 % and 95 % yield, respectively. The internal alkyne 4-octyne (**2c**) also worked well, although higher temperature and longer reaction time were needed. When we explored the scope of arylacetylenes we found good to excellent yields using electron-rich and electron-deficient arylacetylenes. *Para* (**1h**), *meta* (**1i**) and *ortho* (**1j**) tolylacetylenes furnished the corresponding vinylchlorides in excellent yields. It is worth noting that electron deficient arylacetylenes gave increasing amounts of the anti-Markovnikov products (**2n**, **2o**, **2p**, and **2q**). A remarkable example was the heteroaromatic alkyne 2-ethynylpyridine (**1r**), which was expected to quench the reactivity of homogenous cationic gold due to its basic nature, but under our conditions, **1r** furnished the anti-Markovnikov vinylchloride (**2r**) in 70 % yield.

The change of regioselectivity in **2r** could have been caused by the pyridinyl nitrogen acting as a directing group and coordinating with HCl or gold. 3-Ethynylthiophene (**1s**) gave an excellent yield of the corresponding chloro product. The electron deficient internal alkyne ethylphenylpropiolate (**1t**) also worked well, albeit a higher temperature (75°C) was needed, and the yield was modest (66%). In this case, a mixture of E/Z isomers was obtained, possibly due to the isomerization caused by the elevated temperature.

It should be noted that our homogenous gold catalyzed reaction required milder conditions (room temperature) than the recently reported heterogeneous gold catalyzed process, and that the stereochemistry of the addition was different.[14] Due to the milder conditions of our reaction, we expected better functional group tolerance. Indeed, the peptide (**2u**) and derivatized estrone (**2v**) were tolerated under our conditions. The homogenous gold process gave the *anti*-addition pattern (Table 2, **2c** and **2r**), which is consistent with typical homogeneous gold catalysis where cationic gold activates alkyne substrates. On the other hand, the nanogold catalyzed process gave *syn*-addition products, which suggests that nano-gold initially activates HCl rather than the alkyne.[14]

Our strategy for the hydrochlorination of unactivated alkynes was easily expanded to large-scale synthesis, without affecting yield and regioselectivity (Scheme 3a). To examine the synthetic value of the synthesized vinylchlorides, we conducted two classic reactions that use vinyl chlorides as building blocks, namely the Suzuki coupling and the Buchwald–Hartwig amination. In both cases, the desired products were isolated in good yields (Scheme 3, b and c).



Scheme 3. Gram-scale synthesis and the synthetic utility of vinylchlorides.

In conclusion, we have reported the first efficient regioselective homogeneous gold-catalyzed hydrochlorination of unactivated alkynes. We have overcome the traditional incompatibility between conventional cationic gold catalysts and chloride. This method can be easily scaled up, and the reactions can be conducted in the open air.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information

Experimental procedures and characterization data of products. This material is available free of charge via the internet at http://pubs.acs.org.

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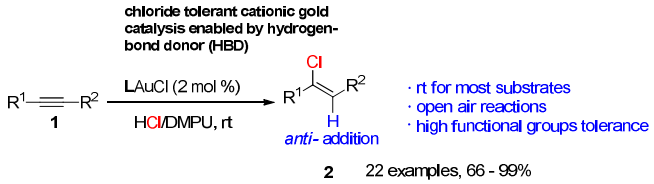
chloride tolerant cationic gold catalysis enabled by hydrogen-bond donor (HBD)
LAuCl (2 mol %)
HCl/DMPU, rt
1
2
anti- addition
· rt for most substrates
· open air reactions
· high functional groups tolerance
22 examples, 66 - 99%