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A Chlorinating Reagent Yields Vinyl Chlorides with High Regioselectivity under Heterogeneous Gold Catalysis

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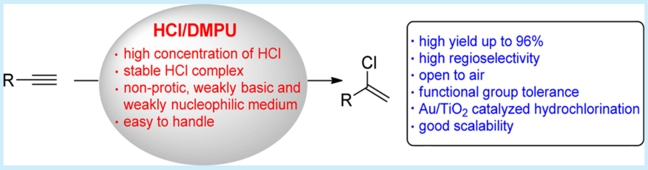
S *Supporting Information*

ABSTRACT: A novel chlorinating reagent with a high concentration of HCl has enabled the highly regioselective hydrochlorination of unactivated alkynes using a commercial nanogold catalyst. No overchlorination or hydration products were formed, and various functional groups were tolerated. This hydrochlorination method could be conducted under open air.



Chlorine-containing compounds are prevalent in natural products, pharmaceuticals, and agrochemicals.[1] They also play a significant role in organic synthesis because of their broad applications as useful intermediates for transition-metal-catalyzed carbon—carbon and carbon—heteroatom coupling reactions such as Buchwald—Hartwig amination[2] and Suzuki—Miyaura coupling.[3] Among various chlorinated compounds, vinyl chlorides stand out as an important group. Compared to traditional synthesis of vinyl chlorides from carbonyl compounds,[4] the direct hydrochlorination of alkynes from HCl is a more straightforward and higher atom-efficiency method. Indeed, several hydrochlorinations of alkynes have been developed using LiCl, $MgCl_2$, AcCl, and TMSCl as a chloride source.[5] However, the direct hydrochlorination of unactivated alkynes using HCl as a chlorine source has been rarely reported. Dai's group found that HCl gas could hydrochlorinate electron-rich phenylacetylenes, although hydrated products were also formed.[6] One remarkable hydrochlorination of alkyne was reported by Derien's group. They developed a highly efficient ruthenium-catalyzed hydrochlorination of alkynes. Both good yield and selectivity were achieved, although strict oxygen- and water-free operation was needed in this strategy.[7] More recently, Corma and coworkers reported a hydrochlorination of alkynes using hydrogen chloride in dioxane and catalytic amounts of gold nanoparticles, but functional group tolerance was not deeply explored.[8]

Searching for an appropriate HCl-based chlorinating reagent is crucial for a direct hydrochlorination reaction. The commercial sources of HCl are usually not very effective chlorinating reagents due to the low activity caused by the relatively low concentration of HCl (Scheme 1). Moreover, the nucleophilicity of chloride in protic mediums such as water and alcohol is greatly reduced.[9] Our group has previously developed a novel nucleophilic fluorinating reagent HF/DMPU based on the concept of hydrogen bond basicity (pK_{BHX}).[10] Considering that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone) is weakly basic and weakly nucleophilic and is a strong hydrogen-bond acceptor, we assumed that it would be also an ideal chlorinating reagent carrier for organic reactions. To our delight, the synthesized HCl/DMPU presents an extraordinarily high mole ratio (2.65) between HCl and DMPU. In contrast, other commercially available HCl solutions have a much lower mole ratio, such as 0.21 for HCl/water, 0.22 for HCl/ether, 0.34 for HCl/dioxane, and 0.42 for HCl/*i*PrOH. The molarity of HCl/DMPU (43% w/w) is 14 M, which is also higher than other commercially available HCl solutions, indicating that HCl/DMPU might exhibit higher activity for nucleophilic chlorination reactions. In addition, as compared with the pK_{BHX} of other HCl solutions such as 0.65 for HCl/water, 1.01 for HCl/ether, 0.73 for HCl/dioxane, and 1.06 for HCl/*i*PrOH, the larger hydrogen-bond basicity (pK_{BHX}) of DMPU (2.79) would also increase the nucleophilicity of

Scheme 1. Comparison of Different Formulations of HCl Solutions

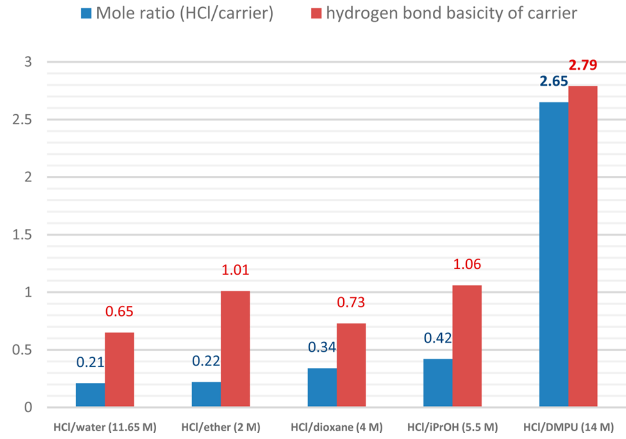


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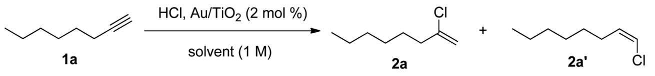
Table 1. Screening of Hydrochlorination of 1-Octyne[a]



entry	HCl (equiv)	solvent	temp (°C)	time (h)	2/2′	yield (%)
1	HCl/Et$_2$O (2)	DCE	80	5	100/0	8
2	HCl/*i*PrOH (2)	DCE	80	5	100/0	15
3	HCl/H$_2$O (2)	DCE	80	5	100/0	4
4	HCl/DMPU (2)	DCE	80	5	90/10	90
5	HCl/DMPU (2)	tol	80	5	88/12	67
6	HCl/DMPU (2)	dioxane	80	5	87/13	93
7	HCl/DMPU (2)	MeCN	80	5	92/8	80
8	HCl/DMPU (2)	*t*-BuOH	80	5	99/1	23
9	HCl/DMPU (2)	DMF	80	5	98/2	55
10	HCl/DMPU (4)	DMF	80	14	98/2	66
11[b]	HCl/DMPU (4)	DMF	80	14	98/2	83
12	HCl/DMPU (4)	DMF	100	14	98/2	85
13	HCl/DMPU (4)	DMA	100	14	98/2	77
14	HCl/DMPU (4)	NMP	100	14	99/1	45
15[c]	HCl/DMPU (4)	DMF	100	14	98/2	68
16[d]	HCl/DMPU (4)	DMF	100	14	98/2	57
17[e]	HCl/DMPU (4)	DMF	100	7	98/2	91
18[f]	HCl/DMPU (4)	DMF	100	14	98/2	71
19[g]	HCl/DMPU (4)	DMF	100	14	100/0	9
20[h]	HCl/DMPU (4)	DMF	100	14	100/0	10
21[i]	HCl/DMPU (4)	DMF	100	14	99/1	46

[a] Both regioselectivity and yield were determined by ^{1}H NMR. [b] Au/TiO$_2$ (4 mol %) was used. [c] [**1a**] = 0.5 M. [d] [**1a**] = 0.2 M. [e] [**1a**] = 2 M. [f] Au/Al$_2$O$_3$ (2 mol %) was used. [g] No Au/TiO$_2$ was used. [h] TiO$_2$ (1 equiv) was used. [i] PPh$_3$AuCl (2 mol %) and AgOTf (2 mol %) were used.

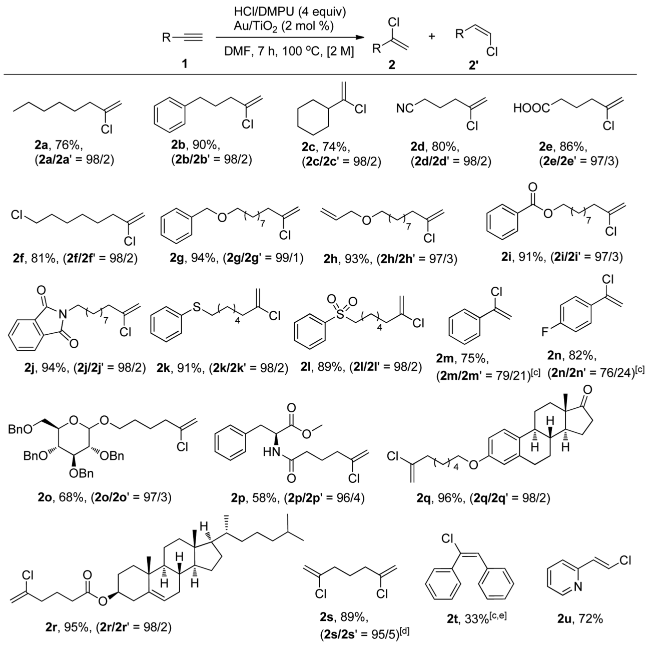
chloride and, meanwhile, form a stable and highly concentrated complex with HCl. Moreover, even at a high mole ratio, we found that the HCl/DMPU complex exhibited less fuming than the common concentrated HCl water solution (HCl/water = 0.21).

Gold catalysis is well-known for its excellent ability to activate C−C unsaturated bonds, thus allowing the generation of a heteroatom−carbon bond via the nucleophilic addition onto the gold-bound π-bond intermediate.[11] Commercially available gold catalysts such as PPh$_3$AuCl are usually stabilized through formation of Au−Cl complexes due to the relatively strong bond energy between gold and chlorine.[12] Thus, silver salts are usually needed to break the strong Au−Cl bond to release active cationic gold species. In our previous work, gold nanoparticles have been successfully used as catalysts for various organic transformations.[13] In particular, we found that the weaker cationic character of gold nanoparticles allowed them to tolerate a strong basic environment, leading, for example, to the hydration of alkynes under basic conditions without affecting acid-sensitive functionalities.[13d] Therefore, we hypothesized that this property may also enable the chloride compatibility of gold nanoparticles. Herein, we are glad to report the first commercially available gold nanoparticle-catalyzed hydrochlorination of unactivated alkynes with HCl/DMPU.

To test the feasibility of our hypothesis, we chose the hydrochlorination of 1-octyne as a model reaction with Au/TiO$_2$ (2 mol %) as the catalyst. Not surprisingly, three commercially available HCl solutions were ineffective for this transformation because of the low concentration of HCl (Table 1, entries 1−3). However, when HCl/DMPU was used, a very high yield of hydrochlorinated product (90%) was observed, and good regioselectivity was also achieved (Table 1, entry 4). To further increase the regioselectivity, we screened different solvents. Nonpolar or less polar solvents such as toluene, dioxane, and acetonitrile did not improve the selectivity (Table 1, entries 5−7). *t*-BuOH provided the desired product with better selectivity yet much poorer yield (Table 1, entry 8). DMF was ultimately considered as the best solvent because of its moderate yield and higher regioselectivity (Table 1, entry 9). More HCl/DMPU (4 equiv) could increase the yield to 66% (Table 1, entry 10). And with more Au/TiO$_2$ (4 mol %), the yield could be further enhanced to 83% (Table 1, entry 11). We found that a higher reaction temperature works equally well (Table 1, entry 12). We also tested other amide types of solvent such as DMA and NMP, but they were inefficient (Table 1, entries 13 and 14). Different reaction concentrations were also screened (Table 1, entries 15−17), and a higher concentration (2 M) gave a 91% yield. Au/Al$_2$O$_3$ was also used in this hydrochlorination reaction, but its efficiency was not as good as Au/TiO$_2$ (Table 1, entry 18). Au/TiO$_2$ was essential for achieving high efficiency for this transformation because when no Au/TiO$_2$ was used or just the support TiO$_2$ was used, only 9% and 10% of products were observed, respectively (Table 1, entries 19 and 20). We found that a homogeneous gold catalyst, using our optimal conditions, was much less effective than heterogeneous gold nanoparticles (Table 1, entry 21).

With optimized conditions in hand, we evaluated the substrate scope. The vinyl chlorides derived from aliphatic terminal alkynes were obtained in good yields and regioselectivities (Scheme 2, **2a**−**2c**). Our hydrochlorination method also exhibited excellent functional group tolerance. Both cyano and carboxylic acid groups could be tolerated (Scheme 2, **2d** and **2e**). A chloro-containing alkyne also provided a corresponding Markovnikov vinyl chloride product in good yield (Scheme 2, **2f**). Both benzyl ether and allyl ether

Scheme 2. Au/TiO$_2$ Catalyzed Hydrochlorination of Alkynes with HCl/DMPU[a,b]

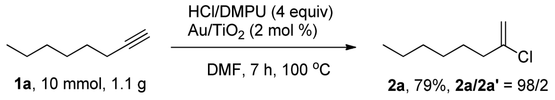


[a]Experiments were performed with **1** (0.4 mmol), HCl/DMPU (43% w/w, 1.6 mmol), Au/TiO$_2$ (2 mol %) in DMF (0.2 mL) at 100 °C. [b]Isolated yields. [c]Not isolated; yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Regioselectivity was dertemined by GCMS. [d]HCl/DMPU (3.2 mmol) was used. [e]Au/TiO$_2$ (4 mol %) was used at 120 °C for 16 h.

substrates worked very well under standard condition (Scheme 2, **2g** and **2h**). Both ester and imide groups remained intact during the hydrochlorination process (Scheme 2, **2i** and **2j**). Sulfane- and sulfone-containing substrates also gave good yields and selectivity without any problem (Scheme 2, **2k** and **2l**). Aromatic terminal alkynes were also examined; however, more anti-Markovnikov products were formed (Scheme 2, **2m** and **2n**). To test the potential of this strategy in the late-stage hydrochlorination of complex molecules, the terminal alkynes attached to biomolecular scaffolds were then examined. A structurally complex glycoside could give corresponding vinyl chloride **2o** without loss of the glycosyl linkage (Scheme 2, **2o**). Protected amino acids such as a phenylalanine derivative were also able to undergo hydrochlorination with a moderate yield (Scheme 2, **2p**). An estrone derivative bearing an alkyne moiety was also a suitable substrate for such a transformation (Scheme 2, **2q**). Lastly, a cholesterol ester derivative could smoothly provide the desired vinyl chloride **2r** with excellent yield and selectivity as well (Scheme 2, **2r**). In addition, we also tried 1,6-heptadiyne, which led to the formation of a divinyl chloride product (Scheme 2, **2s**). Finally, an internal alkyne diphenylacetylene was also examined, which provided the *cis*-vinyl chloride in 33% yield (Scheme 2, **2t**).

It should be noted that when 2-ethynylpyridine was tested, an anti-Markovnikov product was generated, and the *cis*-selectivity of this product is consistent with the *cis*-addition commonly observed in nanogold catalyzed Si–Si or Si–H addition to alkynes or semireduction of alkynes, which suggested that this hydrochlorination of alkynes was, indeed, catalyzed by gold nanoparticles instead of leaching gold species (Scheme 2, **2u**).

Finally, to demonstrate the applicability of our strategy to gram-scale synthesis, we conducted the hydrochlorination of 10 mmol of **1a** under standard condtions; after 7 h, the same yield as that for the reaction in small scale was observed, and the regioselectivity was also not influenced (eq 1).



(1)

In summary, we have found a highly efficient chlorinating reagent in a nonprotic, weakly basic, and weakly nucleophilic medium, DMPU. It has a higher concentration of HCl than commercial HCl sources. These features may be useful in other organic transformations involving HCl. HCl/DMPU was an effective reagent for the synthesis of vinyl chlorides from alkynes using heterogeneous nanogold catalysis. Good yields and regioselectivity were observed, and a variety of functionalities were compatible with this hydrochlorination process. Moreover, this method was easily scaled up and did not require strict oxygen- and water-free conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02101.

Experimental detail and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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