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Au-Catalyzed Addition of Nucleophiles to Chloroalkynes: A Regio- and Stereoselective Synthesis of (*Z*)- Alkenyl Chlorides

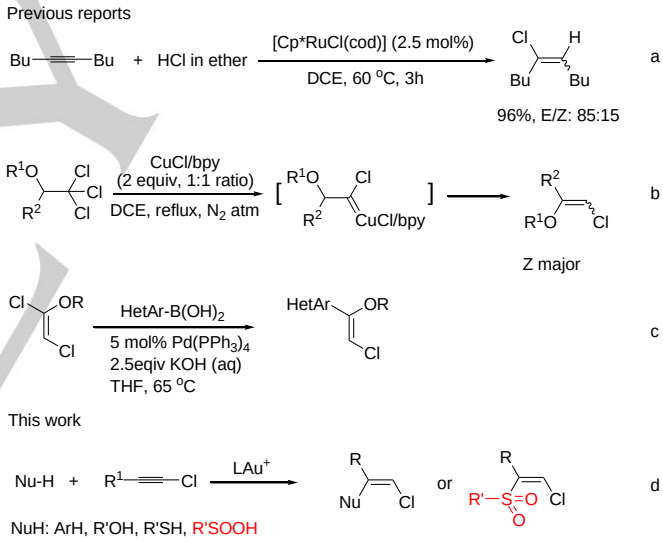
Congrong Liu, *[a] Yunbo Xue, [a] Lianghui Ding, [a] Haiyun Zhang, [a] and Fulai Yang*[b]

Abstract: An unprecedented protocol has been developed for the regio- and stereoselective synthesis of (*Z*)- alkenyl chlorides via the gold-catalyzed addition of nucleophiles to chloroalkynes. In the presence of 1 mol % BrettPhosAuCl, a broad range of nucleophiles smoothly react with aromatic, vinylic or aliphatic chloroalkynes to afford various functionalized (*Z*)- alkenyl chlorides with high to excellent yield and extremely high stereoselectivity.

Introduction

Functionalized olefins are ubiquitous structures in organic chemistry because of its presence in natural and biologically active compounds and are very frequently encountered structural motifs in organic synthesis.[1] In this respect, multisubstituted alkenyl chlorides are valuable intermediates in organic synthesis because of their ability to serve as convenient substrates in hydration, [2] amination [3] and transition metal-catalyzed cross-coupling reactions,[4] such as Buchwald−Hartwig aminations, Sonogashira couplings, Suzuki couplings, Stille couplings and so on. For example, the 2-chloroalkenyl sulfides smoothly couple with aryl/alkylboronic acid with high chemoselectivity and efficience. [5] The 2-chloroalkenyl ethers would be expected to be novel precursors for aryl chloromethyl ketones and a prodrug in the treatment of Alzheimer's disease by hydration. [2] In addition, alkenyl chlorides are commomly found in biologically active natural products. [6] So developing efficient synthetic approaches to construct functionalized alkenyl chlorides is one of the most exciting topics in organic synthesis. [7] Recently, Dérien and co-workers reported a Ru-catalyzed addition of HCl to alkynes for the substituted alkenyl chlorides (Scheme 1a). [8] Ram's group discovered an efficient method for the synthesis of 2-chloroalkeneyl ethers via CuCl/bpy-promoted stereoselective dechlorination of 2,2,2-Trichloroethyl Alkyl Ethers (Scheme 1b). [9] Hultin's group reported a useful method for the formation of (Z)-2-chloroalkenyl ethers via palladium-catalyzed cross coupling of (E)-1,2-dichlorovinyl ethers with aryl boronic acid (Scheme 1c). [10] In spite of the great success achieved so far in this area, some important challenges still remain, such as difficulties in controlling regio- and stereoselectivities, expensive substrates, moderate scope and functional group tolerance. Therefore, a new general, flexible, high stereoselective and regioselective approach for the synthesis of functionalized alkenyl chlorides is still necessary.

Chloroalkynes are one of the most important intermediates and versatile building blocks for synthetic organic chemistry due to their versatile reactivity in a number of chemical transformations. [11] The chloride moiety could also be used for further functionalization, thereby providing a complementary method for the preparation of products that are difficult or impossible to obtain via direct reaction. Although chloroalkynes have versatile applications in organic chemistry, there are very few examples describing the addition of nucleophiles to chloroalkynes.[12] Herein, we report an efficient and facile method for the synthesis of alkenyl chlorides via Au-catalyzed regioselective and stereoselective addition of nucleophiles to chloroalkynes (Scheme 1d).



Scheme 1. Literature reports on the synthesis of differently substituted alkenyl chloride

Results and Discussion

At the outset of this investigation, We examined the addition reaction between anisole (**1a**) and phenylethynyl chloride (**2a**) using 1 mol% $IPrAuNTf_2$ in DCE at 40 °C. Gratifyingly, the reaction gave the desired (Z)- alkenyl chloride (**3a**) in 61% yield (Table 1, Entry 1). Inspired by this result, we further examined the reaction conditions, and the results were summarized in table 1. Gold catalysts based on other ligands were examined, the use of BrettPhos as ligand resulted in the formation of **3a** in 97% yield (Table 1, Entries 2-6). LAuCl is not stable, anionic stabilizer is needed. Replacing $BARF^-$ with other counter anions led to decreased yields (Table 1, Entries 7-9). The reaction was

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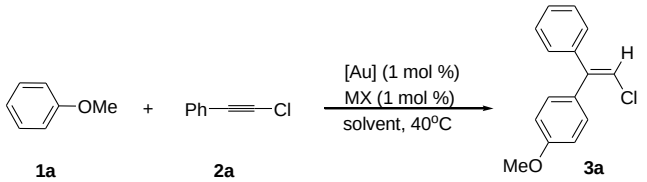
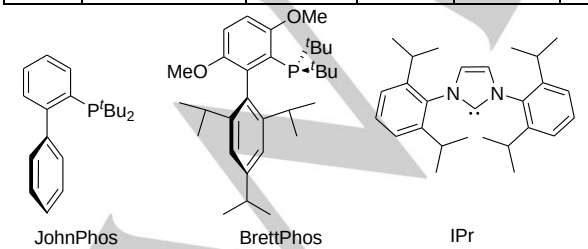
also performed in a common organic solvent other than DCE, but a much lower yield was obtained (Table 1, Entries 10-13). Reducing the reaction temperature led to decreased efficiency (Table 1, Entry 14). In addition, a gram-scale synthesis of (*Z*)-alkenyl chlorides **3a** (2.33 g, 96% yield) was successfully performed according to this protocol.

Table 1 Initial Reaction Conditions Optimization [a]



1a **2a** **3a**

Entry	[Au] (1 mol %)	MX (1mol %)	Solvent	Time (h)	Yield (%)[b]
1	$IPrAuNTf_2$		DCE	10	61
2	$Ph_3PAuNTf_2$		DCE	24	13
3	JohnphosAuCl	NaBARF	DCE	7	75
4	IPrAuCl	NaBARF	DCE	12	82
5	Ph_3PAuCl	NaBARF	DCE	24	18
6	**BrettPhosAuCl**	**NaBARF**	**DCE**	**8**	**97**
7	BrettPhosAuCl	$AgNTf_2$	DCE	12	65
8	BrettPhosAuCl	AgOTf	DCE	12	61
9	BrettPhosAuCl	$AgSbF_6$	DCE	15	49
10	BrettPhosAuCl	NaBARF	MeCN	24	23
11	BrettPhosAuCl	NaBARF	DMSO	24	42
12	BrettPhosAuCl	NaBARF	$MeNO_2$	16	56
13	BrettPhosAuCl	NaBARF	DCM	10	88
14[c]	BrettPhosAuCl	NaBARF	DCE	24	80

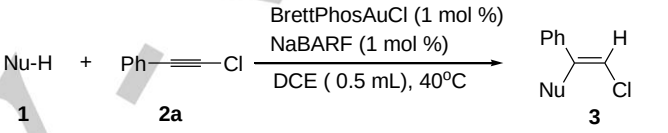


JohnPhos BrettPhos IPr

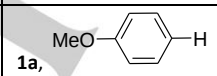
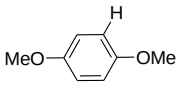
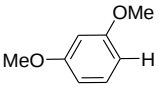
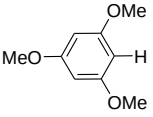
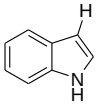
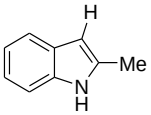
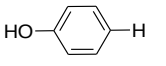
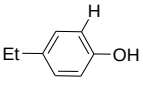
[a] Reaction conditions: anisole **1a** (0.24 mmol), Chloroalkyne **2a** (0.2 mmol), [Au] (1 mol%), MX (1 mol%), solvent (0.5 mL), 40 °C. [b] Isolated yield. [c] Room temperature.

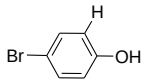
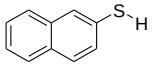
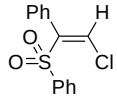
After establishing the optimized conditions (Table 1, entry 6), the scope of this reaction were then investigated in detail with other nucleophiles under the optimal condition. The scope of nucleophiles are very general in the addition with phenylethynyl chloride (Table 2). Appropriately activated arenes could undergo addition with phenylethynyl chloride **2a** to give the corresponding products in very good to excellent yields and with absoluted stereoselectivity (Table 2, Entries 1-9). This protocol was also suitable for alcohols[13] and thiols, and as expected different structural of alcohols/thiols proceeded smoothly with phenylethynyl chloride **2a** to give the corresponding (*Z*)-2-chloroalkenyl ethers/(*Z*)-2-chloroalkenyl thioethers in excellent yields and short reacton times were needed (Table 2, Entries 10–15). Further investigation showed that benzenesulfinic acid also served as suitable substrate in the addition with phenylethynyl chloride **2a**, but the reaction gave the corresponding 2-chloroalkeneyl sulfone (**3p**) instead of sulfinic ester (Table 2, Entry 16).

Table 2 Gold catalyzed regioselective and stereoselective addition of nucleophile **1** to phenylethynyl chloride **2a** [a]



1 **2a** **3**

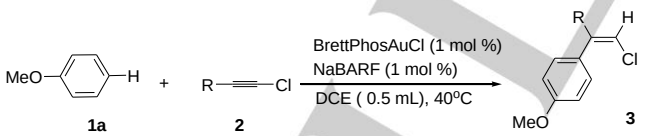
Entry	**1**, Nu-H	**3**	Time (h)	Yield (%)[b]
1	 **1a**,	**3a**	8	97
2	**1b**, 	**3b**	5	89
3	 **1c**,	**3c**	4	95
4	 **1d**,	**3d**	3	99
5	 **1e**,	**3e**	3	85
6	 **1f**,	**3f**	10	80
7	 **1g**,	**3g**	7	90
8	 **1h**,	**3h**	10	86

9	**1i,** 	**3i**	24	80
10[c]	**1j,** EtO−H	**3j**	1	96
11[c]	**1k,** *n*-BuO−H	**3k**	1	99
12[c]	**1l,** N≡CCH$_2$CH$_2$O-H	**3l**	12	90
13[c]	**1m,** BnO-H	**3m**	1	99
14	**1n,** PhS-H	**3n**	0.5	88
15	**1o,** 	**3o**	0.5	91
16	**1p,** PhSOOH	**3p,** 	15	76

[a] Reaction conditions: anisole **1a** (0.24 mmol), Chloroalkyne **2** (0.2 mmol), BrettphosAuCl (1 mol%), NaBARF(1 mol%), DCE (0.5 mL), 40 °C. [b] Isolated yield. [c] alcohol (0.5 mL), without DCE

A broad range of chloroalkynes were found to react with anisole in the presence of 1 mol % BrettPhosAuCl and 1mol % NaBARF to yield structurally diverse (*Z*)- alkenyl chlorides (Table 3).[14] Either electron-donating or electron-withdrawing chloroalkynes were efficiently converted into (*Z*)- alkenyl chlorides in excellent yields with excellent stereoselectivity (Table 3, Entries 1-6). 2-(2-chloroethynyl)naphthalene **2h** reacted smoothly to afford the corresponding product **3w** in 99% yield (Table 3, Entry 7). Notably, the addition anisole to 1-chlorodeca-1,3-diyne **2i** took place only at C-1 and C-2 position in 78% yield (Table 3, Entry 8). Vinylic or aliphatic chloroalkynes also participated well in this reaction. For example, the addition of chloroalkynes **2j** and **2k** afforded the corresponding products **3y** and **3z** in 81% and 70% yields, respectively (Table 3, Entries 9-10).

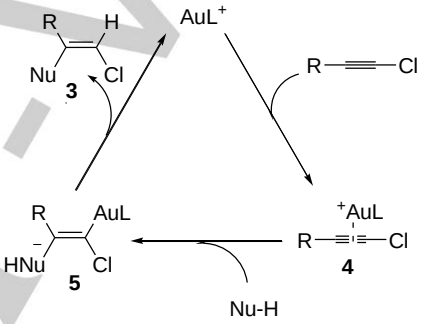
Table 3 Gold catalyzed regioselective and stereoselective addition of anisole **1a** with chloroalkyne **2** [a]



Entry	**2**, R	**3**	Time (h)	Yield (%)
1	**2b**, 4-Me C_6H_4	**3q**	4	98
2	**2c**, 4-Ph C_6H_4	**3r**	7	95
3	**2d**, 4-BrC_6H_4	**3s**	11	94
4	**2e**, 2-Br C_6H_4	**3t**	20	90
5	**2f**, 2,4- $Cl_2C_6H_3$	**3u**	24	86
6	**2g**, 2,4,6-Me_3 C_6H_2	**3v**	24	84
7	**2h**, 2-naphthyl	**3w**	4	99
8	**2i**, *n*-C_6H_{13}CC	**3x**	24	78
9	**2j**, 1-cyclohexenyl	**3y**	24	81
10	**2k**,$PhSO_2CH_2CH_2$	**3z**	30	70

[a] Reaction conditions: anisole **1a** (0.24 mmol), Chloroalkyne **2** (0.2 mmol), BrettphosAuCl (1 mol %), NaBARF (1 mol %), DCE (0.5 mL), 40 °C. [b] Isolated yield.

On the basis of our results and previous studies,[15] we proposed the reaction pathway depicted in Scheme 2 for the steroselective synthesis of functionalized (*Z*)-alkenyl chlorides from chloroalkynes and nucleophiles (Scheme 2). A gold-activated haloalkyne **4** is initially attacked by nucleophile from the back, the chlorine is an electron-withdrawing group, so C-2 is the electrophilic position. The alkenyl gold intermediate **5** is generated, then followed a proton transfer to afford the alkenyl chlorides **3**.



Scheme 2. Proposed mechanism for Au-catalyzed addition of haloalkynes with protic nucleophiles

Conclusions

In summary, we have developed an unprecedented protocol for the regio- and stereoselective synthesis of (Z)- alkenyl chlorides via the gold-catalyzed addition between chloroalkynes and nucleophiles with good to excellent yields. In the presence of 1 mol % BrettPhosAuCl, a broad range of nucleophiles (such as arenes, alcohols, thiols, sulfinic acid) smoothly react with aromatic, vinylic or aliphatic chloroalkynes to afford various functionalized (Z)- alkenyl chlorides with high to excellent yield. Current efforts are directed toward further methodological refinement and synthetic applications.

Experimental Section

General procedure for the gold catalyzed addition of choloalkynes with pronic nucleophiles (Tables 2 and 3): To a solution of protic nucleophile **1** (0.24 mmol) in dry DCE (0.50 mL) were added chloroalkyne **2** (0.20 mmol), BrettPhosAuCl (1.56 mg, 0.0020 mmol) and NaBARF(1.77 mg, 0.0020 mmol) subsequently. The resulting mixture was stirred at 40 °C until no further transformation was detected by TLC analysis. The mixture was cooled to room temperature, and purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (100:0 to 10:1), to give alkenyl chlorides **3**. Parts of the product are known. The regiochemistry and stereochemistry of new products 3a

and 3k was assigned by 2D NOESY analysis, and the regiochemistry and stereochemistry of other new products was assigned by analogy.

Acknowledgements

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Keywords: alkenyl chlorides • chloroalkynes • nucleophiles • gold-catalysis • addition reaction

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[13] When EtOH was 1.2 equiv in DCE, the reaction time 9h and the yield is 87%. Using EtOH as solvents, the reaction time was greatly shorteded to 1h, and the yield was 96%. Alcohols1j-1m are cheap, so these reactions used alcohols as solvents.

[14] Parts of the products are known. The regiochemistry and stereochemistry of new products **3a** and **3k** was assigned by 2D NOESY analysis, and the regiochemistry and stereochemistry of other new products wasassigned by analogy. For details, see the Supporting Information.

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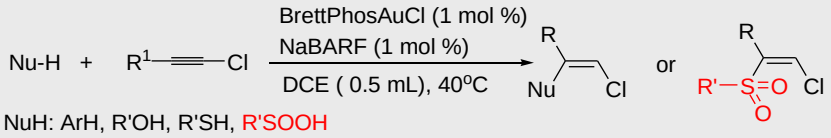
Gold catalysis



An unprecedented protocol has been developed for the regio- and stereoselective synthesis of (*Z*)- alkenyl chlorides via the gold-catalyzed additions between chloroalkynes and protic nucleophiles. In the presence of 1 mol % BrettPhosAuCl, a broad range of protic nucleophiles smoothly react with aromatic, vinylic or aliphatic chloroalkynes to afford various functionalized (*Z*)- alkenyl chlorides with high to excellent yield and extremely high stereoselectivity.

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Au-Catalyzed Addition of Nucleophiles to Chloroalkynes: A Regio- and Stereoselective Synthesis of (*Z*)- Alkenyl Chlorides