Au(I)-Catalyzed Haloalkynylation of Alkenes

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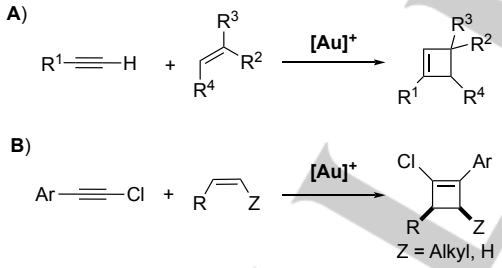
Dedication ((optional))

Abstract: The formal insertion of alkenes into aromatic chloro- and bromoalkynes takes place under cationic gold catalysis. This haloalkynylation reaction can be performed with cyclic, *gem*-disubstituted and monosubstituted alkenes, using BINAP, triazolo[4,3-*b*]isoquinolin-3-ylidene ligands or SPhos, respectively. The products were isolated in moderate to excellent yields and with complete diastereo- and regioselectivity; the halogen atom bonding the more substituted carbon or the alkene. Preliminary experiments showed that the enantioselective haloalkynylation of cyclopentene can be performed with (*S*)-BINAP to afford the insertion products with moderate to good enantioselectivities.

Cationic gold complexes are the most active catalysts for the electrophilic activation of carbon-carbon multiple bonds, being particularly efficient and selective for alkynes.[1] In 2010, Echavarren and co–workers discovered the intermolecular [2+2] cycloaddition of alkenes and alkynes, one of the most fundamental transformations in this field and a valuable tool for the synthesis of cyclobutenes[2] (Scheme 1A). Very recently, the group of Zhang showed that chloroalkynes are also suitable substrates in such [2+2] cycloadditions, leading in this case to valuable chlorocyclobutenes[3] (Scheme 1B). The reaction with bromoalkynes, however, led to a poor yield of the cycloadduct in a single example.



Scheme 1. Gold(I) catalyzed intermolecular [2+2] cycloaddition reactions.

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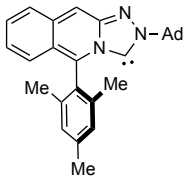
On the other hand, we have been interested in the design of NHCs featuring heterobi(tri)cyclic architectures, which offers opportunities for the modulation of their steric and electronic properties.[4] Within this group, triazolylidenes embedded in tricyclic architectures exhibit an extraordinary π-acceptor character, quantitatively assessed by ^{77}Se NMR[5] in a model ligand **L** (Figure 1).[6] Combined with a high level of steric protection, the electronic properties of this type of NHCs make them particularly attractive for Au(I)-catalyzed reactions, particularly for those in which the activation of the substrate is the rate-limiting step.[7] Moreover, the performance of such ligands has already been shown in challenging asymmetric intermolecular cycloaddition reactions of allenamides.[8]



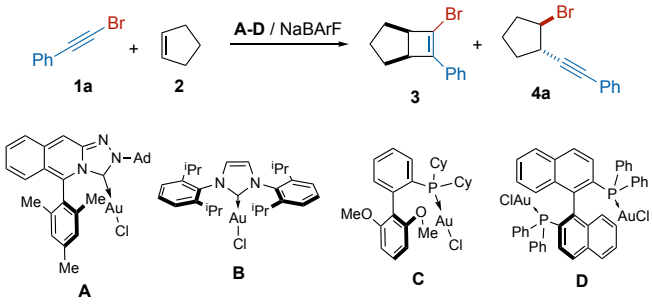
L

^{77}Se NMR [**L**(=Se)]: δ 197 ppm

Figure 1. π-Acidity measurement of heterotricyclic NHC **L**.

On this basis, we decided to explore the behavior of this type of ligands in the Au(I)-catalyzed cycloaddition of bromoalkynes with alkenes. The reaction of (bromoethynyl)benzene **1a** with cyclopentene **2** was chosen as a platform for preliminary studies. The reaction performed with precatalyst **A** (**L**·AuCl) under Zhang's conditions [5 mol% **B** [(IPr·AuCl), IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene] / 10 mol% NaBArF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) in DCE, [**1a**] = 0,1 M, 40 °C] afforded the expected cyclobutene **3**, isolated in 46% yield and, surprisingly, the bromoalkynylation (formal insertion) product **4a** was isolated as a minor component in 16% yield (Table 1, entry 1). To check whether this minor product is also formed under Zhang's experimental conditions, the reaction was also performed with IPrAuCl precatalyst **B**. In fact, a similar amount (15%) of **4a** was obtained in this case, along with the reported [2+2] cycloaddition product **3**, obtained in 41% yield (entry 2). Considering the high synthetic value of the haloalkynylation products and the absence of precedents for this reaction,[9],[10] further efforts were directed to find conditions to increase the yield of the insertion product **4a**. Subtle differences in the ligand structure and reaction conditions proved to have a marked effect in the product distribution. Noteworthy, the reaction performed at room temperature using a higher concentration of **1a** (0.5 M) and only 5 mol% of NaBArF resulted in a much higher proportion of the desired product **4a** (70% yield) although the

Table 1. Gold(I)-catalyzed bromoalkynylation of cyclopentene . Optimization of reaction conditions.[a]



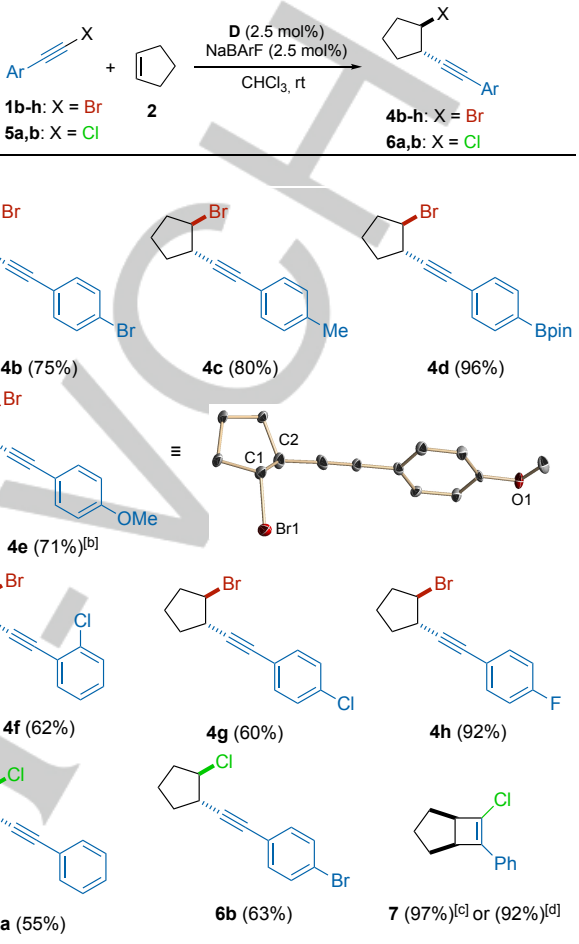
	Catalyst	T [°C]	[**1a**] [mol/L]	Solv.	**3** [%][b]	**4a** [%][b]
1	**A** (5%), NaBArF (10%)	40	0.1	DCE	46	16
2	**B** (5%), NaBArF (10%)	40	0.1	DCE	41	15
3	**A** (5%), NaBArF (5%)	r.t.	0.5	$CHCl_3$	14	70
4	**A** (5%), $AgNTf_2$ (5%)	r.t.	0.5	$CHCl_3$	20	43
5	**A** (5%), $AgSbF_6$ (5%)	r.t.	0.5	$CHCl_3$	--	--
6	**A** (2.5%), NaBArF (2.5%)	r.t.	0.5	$CHCl_3$	6	65
7	**C** (2.5%), NaBArF (2.5%)	r.t.	0.5	$CHCl_3$	13	58
8	**D** (2.5%), NaBArF (5%)	r.t.	0.5	$CHCl_3$	4	69
9[d]	**D** (2.5%), NaBArF (2.5%)	r.t.	0.5	$CHCl_3$	--	**90**

[a] Alkyne:alkene in a 1:3 ratio. Reaction scale 0.2 mmol. [b] Yields of isolated products. [d] Alkyne:alkene in a 1:6 ratio.

cycloaddition product **3** was still formed in 14% yield (entry 3). The nature of the halide scavenger was also important: use of $AgNTf_2$ resulted in a decrease of the amount and proportion of **4a** (entry 4), while $AgSbF_6$ was totally unproductive (entry 5). Finally, the reaction could also be performed with a lower catalyst loading, affording the product **4a** in 65% yield, with only 6% of the cycloaddition product **3** as a minor product (entry 6). Under the optimal conditions, phosphine ligands such as SPhos (precatalyst **C**) and (*rac*)-BINAP (precatalyst **D**) were also tested. Although the use of SPhos-derived **C** did not improve the previous results (entry 7), BINAP derivative **D** allowed to isolate **4a** in 69% yield, while the amount of cycloadduct **3** was further reduced to a 4% yield (entry 8). Finally, this result could be significantly improved using the monocationic gold complex from **D** and increasing the alkene excess (entry 9), thus enabling the isolation of **4a** in an excellent 90% yield.

The reaction could be extended to aromatic bromoalkynes **1b-h** with different substitution patterns (Table 2). Electron-withdrawing or electron donating groups on the aromatic ring were well tolerated, and the bromoalkynylation products **4b-h** were obtained in good to excellent yields and, in all cases, with perfect *trans* diastereoselectivity. X-Ray diffraction analysis of **4e**

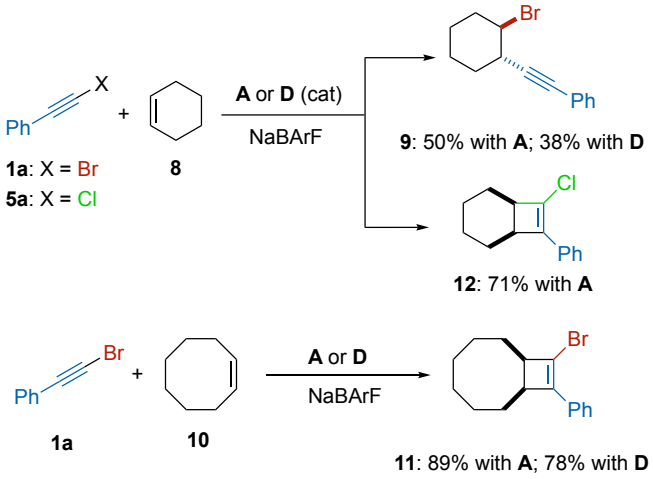
Table 2. Gold(I)-catalyzed haloalkynylation of cyclopentene **2**.[a]



[a] Alkyne:alkene in a 1:6 ratio. Isolated yields. [**3**] = 0.5 M in $CHCl_3$. [b] Reaction carried out at 0 °C. [c] Catalyst: 5 mol% **A** / 10 mol% NaBArF. [d] Catalyst: 5 mol% **B** / 10 mol% NaBArF.

confirmed the relative configuration.[11] Finally, these conditions allowed to perform chloroalkynylations with (chloroethynyl)benzenes **5a** and **5b** to afford the corresponding insertion products **6a** and **6b**, although in somewhat lower yields. In sharp contrast, the use of NHC-based precatalysts **A** and **B** led exclusively to the cycloaddition product **7** in excellent yields.

Interestingly, the reaction is very sensitive to the ring size of the cyclic alkene. Thus, the reaction of bromoethynylbenzene **1a** with cyclohexene **8** afforded the insertion product **9** in a lower yield than cyclopentene (38% versus 90% yield, Scheme 2). Furthermore, cyclooctene **10** reacted with **1a** to afford exclusively the [2+2] cycloaddition product **11** in 78% yield. In these two cases, our NHC-based precatalyst complex **A** was far more efficient than BINAP derivative **D**, affording products **9** and **11** in 50% and 89% yield, respectively. In contrast, no insertion product was observed in the reaction of choroalkyne **7a** with cyclohexene **10**. Catalyst **D** led to a complex mixture of products, while NHC-based catalyst **A** produced cyclobutene **12** in a 71% yield, highlighting again the sensitivity of the reaction to ligand effects.

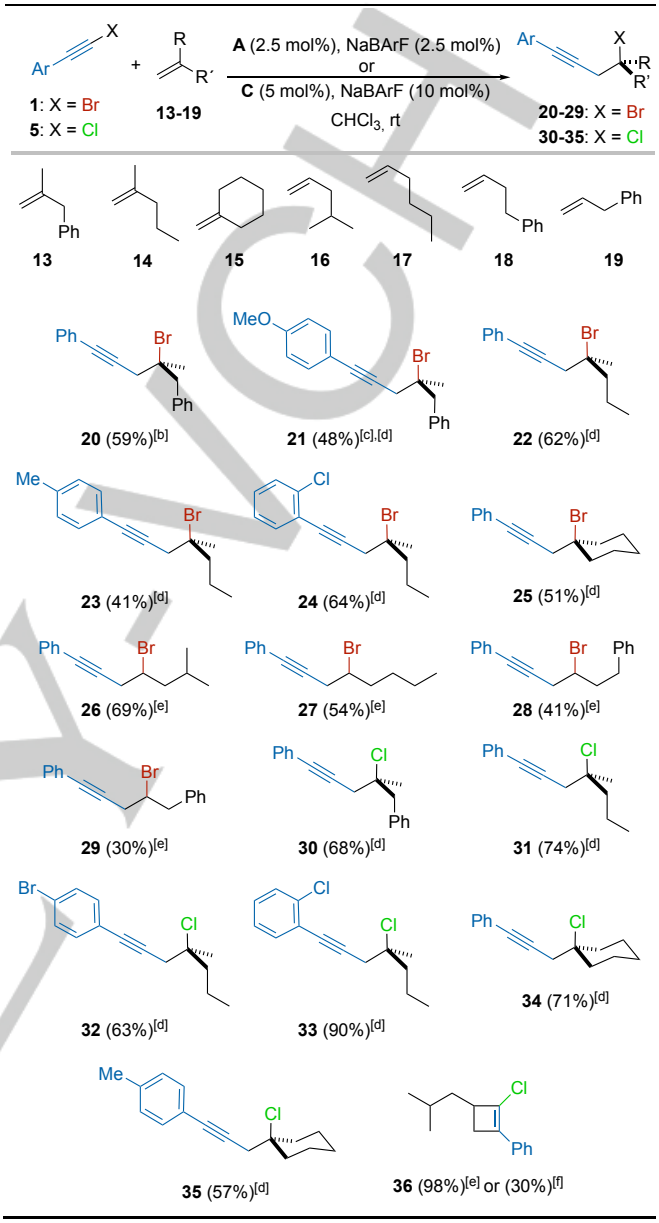


Scheme 2. Reactions of cyclohexene and cyclooctene with haloalkynes.

We envisaged the synthesis of functionalized halogenated compounds featuring a quaternary carbon as an interesting application of the methodology. With this aim, *gem*-disubstituted terminal alkenes **13-15** were made to react with aromatic bromoalkynes **1**. Noteworthy, NHC-Au(I) complex **A** proved to be the only effective precatalyst, leading to the formation the desired bromoalkynes **20-25**. In all cases, a complete regioselectivity is observed: the bromine atom being incorporated into the more substituted carbon of the alkene (Table 3). The extension of the method to monosubstituted alkenes proved to be particularly challenging. The reaction between (bromoethynyl)benzene **1a** and 4-methylpent-1-ene **16** was chosen as model system. Under previously optimized conditions for cyclopentene (2.5 mol% catalyst **D**) or 1,1-disubstituted alkenes (2.5 mol% catalyst **A**), only complex mixtures were observed and the insertion product **26** was isolated in very low yields. Fortunately, though, an additional optimization (see Supporting Information for details) served to identify SPhos-derived precatalyst **C** as the best option. Thus, a combination of **C** (5 mol%) and NaBArF (10 mol%) was used to obtain the product **26** in a satisfactory 69% yield. The reaction with other alkenes **17-19** afforded the corresponding adducts **27-29** in low to moderate yields.[12]

The reaction of *gem*-disubstituted alkenes **13-15** could also be extended to (chloroethynyl)benzenes **5**. Using again gold complex **A** as the precatalyst, the corresponding insertion products **30-35** were obtained, as in the previous cases, with full regioselectivity. Remarkably, higher yields (up to 90%) than for the brominated analogues were regularly observed. We also tried to perform the reaction of chloroalkyne **5a** with monosubstituted alkene **16** but, unexpectedly, no insertion product could be observed in this case, regardless of the catalyst used. The cyclobutene compound **36** was isolated in 98% or 30% yield with precatalysts **A** or **C**, respectively.

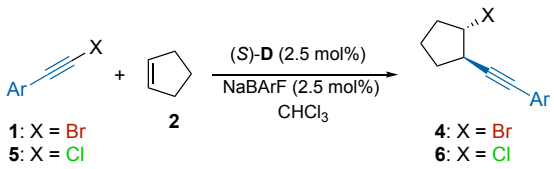
Table 3. Gold(I)-catalyzed haloalkynylation of terminal alkenes.[a]



[a] Alkyne:alkene in a 1:6 ratio. Isolated yields. [alkyne] = 0.5 M in $CHCl_3$. [b] Catalyst: 5 mol% **A** / 5 mol% NaBArF. [c] Reaction carried out at 0 °C. [d] Catalyst: 2.5 mol% **A** / 2.5 mol% NaBArF. [e] Catalyst: 5 mol% **A** / 10 mol% NaBArF. [f] Catalyst: 5 mol% **C** / 10 mol% NaBArF.

Finally, we decided to explore the enantioselective version of the reaction. Although no significant asymmetric inductions have been observed so far in the haloalkynylation of terminal alkenes, preliminary experiments demonstrated that the insertion of cyclic alkenes can be performed with good enantioselectivities. Thus, the model reaction between **1a** and **2** (Table 4) was used as a model to perform initial screening of chiral ligands and reactions conditions (see Supporting information for details). From this study, (*S*)-BINAP$(AuCl)_2$ complex (*S*)-**D** turned out to be the best option, affording enantioenriched (*R*,*S*)-**4a** in a satisfactory 94:6

Table 4. Enantioselective haloalkynylations.[a]



1: X = Br
5: X = Cl

2

4: X = Br
6: X = Cl

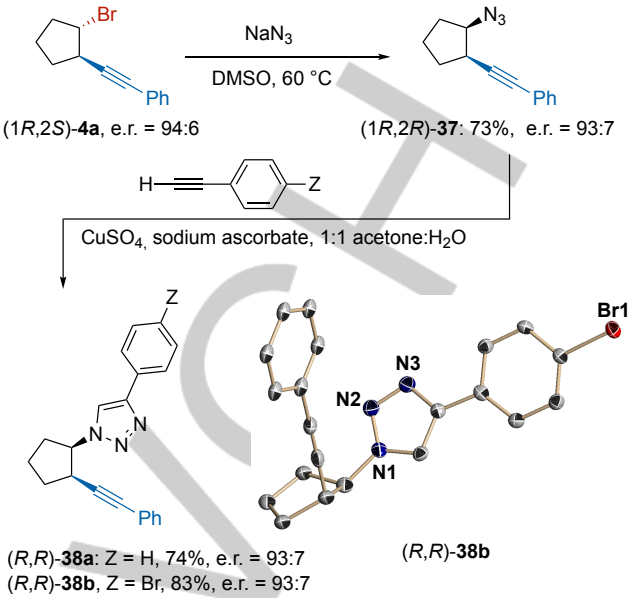
Entry	Product	T [°C]	*t* [h]	Yield (%)[b]	*er* (%)[c]
1	(*R*,*S*)-**4a**	–20	72	89	94:6
2	(*R*,*S*)-**4b**	0	96	65	90:10
3	(*R*,*S*)-**4c**	–20	48	57	94:6
4	(*R*,*S*)-**4e**	–20	10	71	89:11
5	(*R*,*S*)-**4g**	0	72	66	89:11
6	(*R*,*S*)-**4h**	0	96	75	90:10
7	(*R*,*S*)-**6a**	r.t.	48	55	80:20
8	(*R*,*S*)-**6b**	0	96	50	85:15

[a] Alkyne:alkene in a 1:6 ratio. Reaction scale 0.2 mmol. [b] Yields of isolated products. [c] Determined by chiral HPLC.

e.r. at –20 °C. Asymmetric bromoalkynylations with other substrates **1** also afforded the corresponding products **4** in good enantioselectivities (entries 2-6). Enantioselective chloroalkynylations, however, were less efficient; the corresponding insertion products **6a** and **6b** were obtained in somewhat lower yields and enantioselectivities (entries 7 and 8).

The synthetic versatility of compounds **4** relies in good part on the possibility of performing nucleophilic substitutions, a challenging transformation avoiding HBr elimination. Fortunately, the reaction of **4a** with NaN_3 in DMSO at 60 °C led to the desired product (*R*,*R*)-**37** in 73% yield (Scheme 3). As expected, the reaction proceeds with inversion of the configuration at C(2) and without erosion of the enantiomeric purity. Subsequent 1,3-dipolar cycloaddition between azide (*R*,*R*)-**37** and phenylacetylene or *p*-bromophenylacetylene afforded triazoles (*R*,*R*)-**38a** and (*R*,*R*)-**38b** in 74% and 83% yield, respectively. Slow diffusion of pentane into a solution of the latter in dichloromethane afforded crystals suitable for single-crystal X-ray diffraction analysis, which was used to assign the absolute (*R*,*R*) configuration.[11]

In summary, the Au(I)-catalyzed haloalkynylation of unfunctionalyzed alkenes can be performed in a highly diastereo- and regioselective manner by choice of suitable ligands. Moreover, the asymmetric haloalkynylation of cyclopentene afforded the corresponding insertion products with good enantioselectivities.



Scheme 3. Synthesis of triazole derivatives and ORTEP drawing of (*R*,*R*)-**38b**.

Experimental Section

Haloalkynylation of cyclopentene **2**: To a mixture of haloalkyne **1** or **5** (0.2 mmol) and BINAP-$(AuCl)_2$ **D** (2.5 mmol%, 5.4 mg) in anhydrous chloroform (0.4 mL) was added cyclopentene (**2**) (1.2 mmol, 81.7 mg, 106 µL). After stirring for 10 minutes at room temperature, NaBArF (2.5 mmol%, 4.4 mg) was added. The reaction mixture was stirred until GC monitoring indicated total consumption of the starting haloalkyne. A drop of Et_3N was then added and the mixture was concentrated, in vacuo. Purification by flash column chromatography afforded the products **4** or **6**.

Acknowledgements

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Keywords: keyword 1 • keyword 2 • keyword 3 • keyword 4 • keyword 5

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[9] To the best of our knlowledge, there is a single report limited to the bromoalkynylation of norbornene via Pd(II) catalysis: Y. Li, X. Liu, H. Jiang, B. Liu, Z. Chen, P. Zhou, *Angew. Chem. Int. Ed.* **2011**, *50*, 6341-6345.

[10] While this manuscript was in preparation the chloroalkynylation of 1,1-disubstituted alkenes was reported: M. Kreuzahler, G. Haberhauer, *J. Org. Chem.* **2019**, *84*, 8210-8224. In contrast with our results, a computational study within this paper suggests that the reaction with internal alkenes cannot be performed. Additionally, bromoalkynylation products were also isolated during mechanistic studies performed by Echavarren and co–workers on the gold–catalysed cross–coupling of bromoalkynes with allylsilanes: M. E. de Orbe, M. Zanini, O. Quinonero, A. M. Echavarren, *ACS Catal.*, **2019**, *9*, 7817-7822. In both cases, a short scope and moderate yields limited the synthetic value of the methodology.

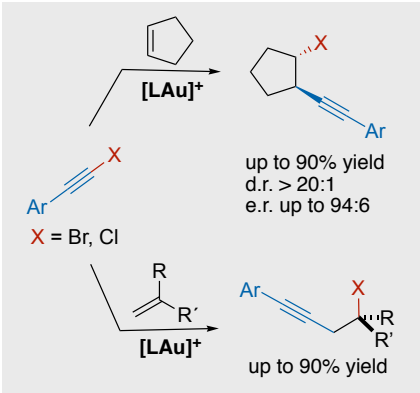
[11] CCDC 1954161 and 1954160 contain the supplementary crystallographic data for **4e** and (*R*,*R*)-**38b**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[12] Analysis by GC of the crude reaction mixtures showed elimination of HBr from bromoalkynylated products. In fact, the product of HBr addition to the triple bond of **26** was isolated.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Formally inserted: Cyclic and terminal alkenes react with bromo- and chloroalkynes under cationic gold catalysis to afford haloalkynylation products. Appropriate choice of ligands and conditions enabled the obtention of valuable haloalkynes with high levels of diastereo- regio- and enantioselectivity.



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