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Gold(I)-catalyzed arylmethylation of terminal alkynes

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AuCl/AgOTf catalyzes the reaction of terminal alkynes with aryl trichloroacetimidate to afford arylmethylation products in moderate to good yields.

Gold-catalyzed reactions have attracted considerable attention in recent years.[1] The research activities in this field so far have been mostly concentrated on the reaction of gold-activated alkynes functioning as electron-deficient species to accept nucleophilic attack (Fig. 1. path ***a***). The alternative process, namely the gold-alkyne species functioning as nucleophile (path ***b***), is much less developed except simple protonation or elimination.

Recently, gold-catalyzed C–C bond formation via the reaction of terminal alkyne C–H bonds has appeared in the literature and opened up new possibilities.[2] Li and co-workers have reported a gold-catalyzed three-component reaction of aldehyde, alkyne, and amine.[3] In this reaction a gold acetylide species is proposed as the reactive intermediate, which adds to C=N bond of iminium ion. More recently, they further reported a Au-catalyzed cascade addition/cyclization of terminal alkynes with *ortho*-alkynylaryl aldehyde, in which gold (I)-acetylide addition to C=O bond is suggested as the C–C bond forming step in the reaction mechanism.[4] On the other hand, Wang and Zhang have reported a Au(III)-catalyzed acyl migration of propargylic esters in which the intramolecular attack of nucleophilic Au(III)–C(sp^2) to C=O bond is supposed as the key step in the reaction mechanism.[5] These results indicate that the nucleophilicity of Au–C bond can be exploited in the formation of C–C bond.

Besides nucleophilic addition to C=N or C=O bonds, S_N2-type substitution can be reasonably considered as another possibility for the reaction of the intermediate containing nucleophilic Au–C bond. However, gold-catalyzed reaction based on this process has been rare.[6] As far as our knowledge is concerned, the nucleophilic substitution of Au-acetylide in catalytic process has not been documented in the literature.

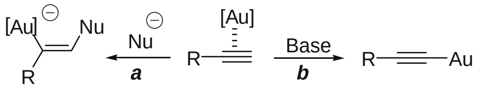
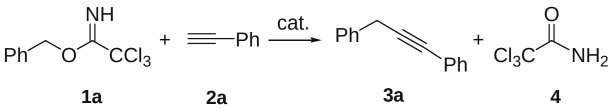


Figure 1. Gold-catalyzed reaction of alkyne.

To achieve this goal, an electrophilic reaction partner containing a suitable leaving group is pivotal. After some initial examination of the electrophiles, it turned out that trichloroacetimidoxyl group was an excellent leaving group for this purpose.[7] Herein we report the AuOTf-catalyzed reaction of terminal alkyne with benzylic trichloroacetimidate. The reaction, in which the nucleophilic substitution of protonated trichloroacetimidoxyl group by gold-acetylide species is supposed to be the key step, gave arylmethylation products in moderate to good yields (Scheme 1).

At the outset, the reaction of benzyl trichloroacetimidate **1a** and phenylacetylene **2a** with 5 mol % AuCl and AgOTf as catalysts at room temperature in DCE was examined (Table 1). After 48 h, 1,3-diphenylpropyne **3a** was isolated in low yield (entry 1), and



Scheme 1. Catalytic reaction of terminal alkyne with benzylic trichloroacetimidate.

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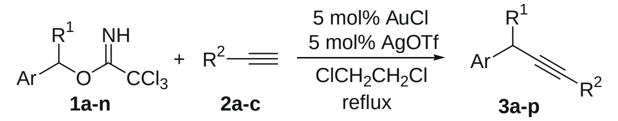
Table 1
Reaction of **1a** with **2a** under various catalytic conditions

Entry	Cat. (5 mol %)	Solvent	T (°C)	t (h)	Yield[a] (%)
1	AuCl + AgOTf	DCE	25	48	13
2	AuCl + AgOTf	DCE	80	3	65
3	AuCl + AgOTf + Et$_3$N	DCE	80	5	N.R.[b]
4	Ph$_3$PAuCl + AgOTf	DCE	80	5	53
5	AuCl	DCE	80	5	N.R.[b]
6	AgOTf	DCE	80	12	*Trace*
7	AgBF$_4$	DCE	80	5	15
8	AuCl$_3$	DCE	25	5	—[c]
9	CuI	DCE	80	5	N.R.
10	PtCl$_2$	DCE	80	5	*Trace*
11	Pd(PPh$_3$)$_4$ + CuI	DCE	80	5	*Trace*
12	AuCl + AgOTf	Dioxane	100	5	15
13	AuCl + AgOTf	CHCl$_3$	61	5	32
14	AuCl + AgOTf	MeCN	25	5	*Trace*
15	AuCl + AgOTf	C$_6$H$_6$	80	0.5	60[d]
16	TfOH	DCE	80	5	17

[a] Isolated yields.
[b] No reaction.
[c] Reaction gave complex mixture.
[d] Diphenylmethane was the isolated product.

Table 2
Gold(I)-catalyzed arylmethylation of terminal alkynes



Entry	Trichloroacetimidate (**1**, Ar, R^1)	Alkyne (**2**, R^2)	t (h)	Yield[a] (%)
1	**1a**, C$_6$H$_5$, H	**2a**, C$_6$H$_5$	3	65
2	**1b**, o-ClC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	54
3	**1c**, o-BrC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	62
4	**1d**, o-IC$_6$H$_4$, H	**2a**, C$_6$H$_5$	3.5	63
5	**1e**, m-ClC$_6$H$_4$, H	**2a**, C$_6$H$_5$	10	79
6	**1f**, m-BrC$_6$H$_4$, H	**2a**, C$_6$H$_5$	10	85
7	**1g**, p-FC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	55
8	**1h**, p-ClC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	69
9	**1i**, p-BrC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	63
10	**1j**, m-Me-p-BrC$_6$H$_3$, H	**2a**, C$_6$H$_5$	3	84
11	**1k**, o-MeC$_6$H$_4$, H	**2a**, C$_6$H$_5$	4	66
12	**1l**, p-PhC$_6$H$_4$, H	**2a**, C$_6$H$_5$	5	48
13	**1m**, p-^{t}BuC$_6$H$_4$, H	**2a**, C$_6$H$_5$	3	66
14	**1n**, C$_6$H$_5$, C$_6$H$_5$	**2a**, C$_6$H$_5$	4	55
15	**1a**, C$_6$H$_5$, H	**2b**, p-BrC$_6$H$_4$	4	57
16	**1a**, C$_6$H$_5$, H	**2c**, n-C$_4$H$_9$	4	30
17	**1o**, p-NO$_2$C$_6$H$_4$, H	**2a**, C$_6$H$_5$	5	0[b]
18	**1p**, 6-MePy, H	**2a**, C$_6$H$_5$	5	0

[a] Isolated yields after column chromatography.
[b] Starting materials were recovered.

most of **1a** was recovered. Trichloroacetamide **4** was also identified in GC–MS. When the reaction was conducted in refluxing DCE, **1a** was all consumed to afford **3a** in moderate yield (entry 2). When triethylamine was added in the reaction as base, no reaction occurred (entry 3). Replacing the AuCl with AuPPh$_3$Cl gave similar result (entry 4), but no reaction was observed when AuCl alone was used as the catalyst in the absence of AgOTf (entry 5). With Ag(I) salt as the only catalyst, trace amount or low yield of **3a** could be obtained (entries 6 and 7). Reaction with AuCl$_3$ alone resulted in a complex mixture (entry 8). Some other catalysts were also examined. CuI and PtCl$_2$ were found to be not effective in the reaction (entries 9 and 10), neither did the Sonogashira coupling catalyst system[Pd(PPh$_3$)$_4$+CuI] (entry 11).

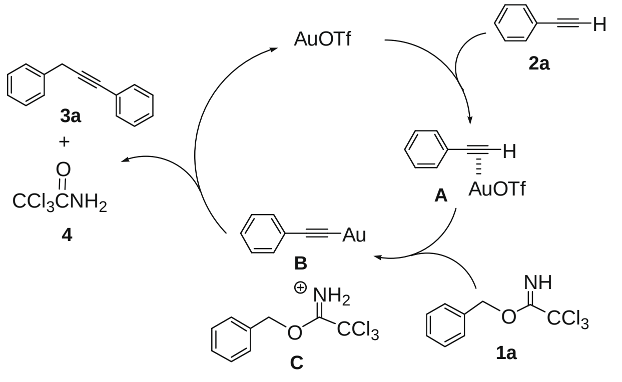
With AuCl/AgOTf catalytic system, the solvent effects were examined and DCE was found to be the most suitable solvent (entries 12–14). It was interesting to note that when the reaction was carried out in benzene, the expected **3a** was not formed, instead, diphenylmethane was isolated in 60% yield (entry 15). The formation of diphenylmethane is likely due to Friedel–Crafts reaction of Au(I)-activated **1a** and benzene. It was worth noting that in all experiments described above the formation of metallic gold or silver was not observed and the reaction remained homogenous. Finally, it was also noted that protic acid TfOH could catalyze the same reaction, but affording **3a** in much lower yield (entry 16).

Under the optimized condition, the scope of the reaction was examined with a variety of substrates (Table 2).[8] The trichloroacetimidate substrates **1b**–**n** with alkyl and halide substitution in the phenyl ring could all react smoothly to give moderate yields, as shown in Table 2. Under the same condition, 1,3,3-triphenyl-1-propyne[9] could be prepared by using diphenylmethanol-derived trichloroacetimidate **1n** (entry 14). However, the trichloroacetimidate substrates with p-nitrophenyl and pyridine substituents failed to react under the same condition (entries 17 and 18). The scope of alkyne substrate was also examined. Substitution on the phenyl ring of phenylacetylene seems to not effect the reaction (entry 15). Aliphatic alkynes could react similarly, but the yield was low (entry 16).

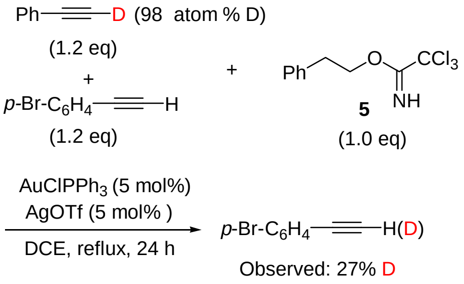
Benzylacetylene and its derivatives are versatile synthetic intermediates, and they are usually prepared by nucleophilic attack of phenylacetylenyl anion to benzyl halide or p-toluenesulfonate,[10] or by transition metal-catalyzed cross-coupling reactions with organometallic reagents.[11] These reactions are generally conducted in strong basic conditions and thus the functional group compatibility is limited. The gold-catalyzed arylmethylation reaction of terminal alkynes described above is under mild and almost neutral conditions.

A mechanistic proposal for this reaction is shown in Scheme 2. The coordination of the gold catalyst with alkynes raises the acidity of the terminal proton of **A**. The basicity of the nitrogen in the benzyl trichloroacetimidate is strong enough to remove the terminal proton from Au-activated alkyne **A**, presumably with the formation of gold acetylide intermediate **B**.[2,3] On the other hand, the trichloroacetimidoxyl group of **1a** turns to be a better leaving group after being protonated.[12] The nucleophilic gold acetylide attacks the benzyl position to form a new carbon–carbon bond. Trichloroacetamide is released as a leaving group, which is neutral and does not interfere with the activity of gold catalyst. In this mechanism, the trichloroacetimidoxyl group in the substrate plays two pivotal roles: the nitrogen atom can function as a base to generate gold acetylide through deprotonation of gold-activated terminal alkyne, the protonated trichloroacetimidoxyl group then becomes a very good leaving group, which accepts the attack of gold acetylide.

The key issue of the reaction mechanism of this investigation is the generation of Au-acetylide as reactive intermediate. If Au-



Scheme 2. A plausible mechanism.



Scheme 3. Deuterium exchange experiment.

acetylide is indeed involved, there will be exchange of protons from different terminal alkynes. Previous study indicated that β-phenylethyl trichloroacetimidate **5** did not react with terminal alkynes under the identical reaction conditions. Thus, **5** was utilized as a base in a H/D exchange experiment as shown in Scheme 3. If Au-acetylides are generated, the theoretical ratio of deuterium to hydrogen in *p*-bromophenylacetylene will be around 33.33% when complete equilibrium is reached. The observed deuterium content of the recovered *p*-bromophenylacetylene is around 27%. For comparison, the H/D exchange experiment was also carried out with TfOH as catalyst under otherwise identical conditions. In such case, no H/D exchange was observed. The results of the H/D exchange experiment are consistent with proposed reaction mechanism in which gold acetylide is generated as reactive intermediate.[13]

In conclusion, arylmethylation of terminal alkynes has been realized by the catalysis of Au(I) complex. The process is simple and mild and generates benzylacetylene and its derivatives in good yields. Moreover, the study demonstrates the possibility of Au–C bonds being exploited as nucleophiles in substitution reactions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.067.

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