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Gold(I)-Catalyzed Haloalkynylation of Aryl Alkynes: Two Pathways, One Goal

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Abstract: *Haloalkynylation reactions represent an efficient method for the simultaneous introduction of a halogen atom and an acetylenic unit. For the first time, we are reporting a gold(I)-catalyzed haloalkynylation of aryl alkynes which delivers exclusively the cis addition product. This protocol enables the simple synthesis of conjugated and halogenated enynes in yields up to 90%. Notably, quantum chemical calculations reveal an exceptional interplay between the regioselective attack at the chloroacetylene: No matter which C-C bond is formed, always the same enyne product is formed. This is only possible via rearrangement of the corresponding skeleton. Hereby, one reaction pathway proceeds via a chloronium ion with a subsequent aryl shift; in the second case the corresponding vinyl cation is stabilized by a 1,3-chlorine shift.* ^{13}*C-labeling experiments confirmed that the reaction proceeds via both reaction pathways.*

The development of novel and highly efficient carbon-carbon bond forming reactions for the design of complex molecules is a fundamental principle in organic chemistry.[1] One of the most important substance class are halogenated compounds. Since the halogen atom is usually discarded in the course of carbon-carbon bond forming reactions, the development of C-C bond forming reactions in which the halogen atom remains in the product, is of great interest. So far, only a few examples have been reported; some of these reactions are starting from haloacetylenes.[2] The latter are readily accessible[2b] and decompose, with the exception of fluoroacetylenes[3], only at higher temperatures.[4] Until recently, the simultaneous addition of one halogen atom and one alkyne unit (haloalkynylation) to a carbon-carbon double bond was only possible for norbornene systems.[5] We were able to

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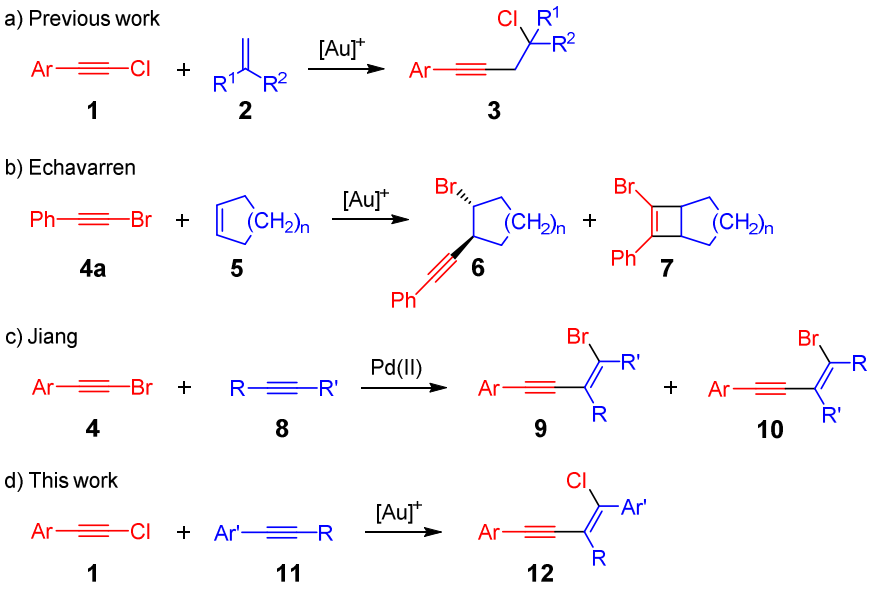
demonstrate for the first time that the chloroalkynylation of 1,1-disubstituted alkenes (**2**) can be achieved via gold(I) catalysis[6] leading to the homopropargyl chlorides **3** in good yields (Scheme 1a).[7] This reaction principle can also be extended to bromoacetylenes (**4**) and 1,2-disubstituted alkenes **5** (Scheme 1b)[8] and represents one of the few examples for gold(I)-catalyzed reactions where the triple bond remains after the reaction.[9],[10] In the case of the gold(I)-catalyzed haloalkynylation of cyclic alkenes a side reaction, namely the already known gold(I)-catalyzed [2+2] cycloaddition,[11] takes place (Scheme 1b).[8] The bromoalkynylation of cyclic alkenes proceeds via a *trans* addition and can also be accomplished enantioselectively by the use of chiral gold(I) catalysts.[12]

The gold-catalyzed haloalkynylation of internal alkynes has not been described so far; only a palladium-catalyzed variant exists.[13] However, the application of this protocol is primarily restricted to hydroxy-alkyl substituted triple bonds.[13a] In case of dialkyl- and arylalkyl alkynes always both regioisomers (conjugated and cross-conjugated) are formed in almost the same ratio (Scheme 1c).[13a] Herein, we study the haloalkynylation of aryl alkynes via gold catalysis and are able to demonstrate that this reaction leads to the highly selective formation of the conjugated and halogenated enynes in yields up to 90% (Scheme 1d). Mechanistic investigations reveal that the product is formed via two extraordinary and complementary reaction pathways.



Scheme 1. Gold(I)-catalyzed haloalkynylation of 1,1-disubstituted (a) and 1,2-disubstituted (b) alkenes. Palladium(II)- and gold(I)-catalyzed addition of haloarylacetylenes **4** and **1** to internal alkynes (c and d).

For the investigation of the haloalkynylation reaction, chloroarylacetylene **1a** was chosen as model system (Table 1) in the first step. The electronegative fluorine atom, which is attached

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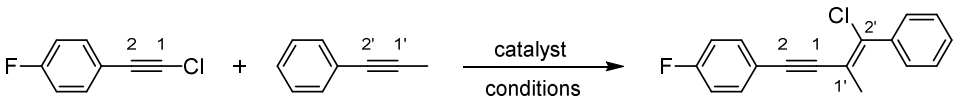
to the *para* position of the aryl alkyne unit, should slow down the competing dimerization[10] of the chloroarylacetylene **1a**. Alkyne **11a** was chosen as simple representative for the aryl alkynes. Dry 1,2-dichloroethane (DCE) was used as reaction solvent. The usage of an appropriate concentration of the chloroarylacetylene **1a** is mandatory as higher concentrations accelerate the dimerization[10], whereas lower concentrations favor the hydration of the chloroarylacetylene.[14] Already the first attempt with a ratio of 1:1 for the starting materials (**1a** and **11a**) and 5 mol% [JohnPhos(AuNCMe)]SbF_6[15], which already gave good results for the previously reported chloroalkynylation of 1,1-disubstitued alkenes (see Scheme 1a),[7] led to a single product with a yield of 56% (entry 1 in Table 1). The ^{1}H NMR spectrum of the crude product does not show any significant byproducts that are formed in higher yields. An analysis via one- and two-dimensional NMR spectroscopy indicates that the reaction product is the conjugated *cis* addition product **12a** (Figures S16-S17).

Table 1. Optimization of the reaction conditions for the gold(I)-catalyzed chloroalkynylation of alkyne **11a**.



1a **11a** **12a**

Entry	**1a** : **11a**	Catalyst	Yield [%]
1	1 : 1	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)[15]	56
2	1 : 1.5	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	66
3	1 : 1.5	JohnPhosAuNTf_2 (5 mol%)[16]	67
4	1 : 1.5	CyJohnPhosAuCl (5 mol%), $NaBArF_{24}$ (5 mol%)[17]	56
5	1 : 1.5	CyJohnPhosAuCl (5 mol%), $AgSbF_6$ (5 mol%)	67
6	1 : 1.5	CyJohnPhosAuCl (5 mol%), $AgNTf_2$ (5 mol%)	65
7	1 : 1.5	*t*BuXPhosAu(NCMe)SbF_6[18]	53
8	1 : 1.5	*t*BuXPhosAuNTf_2[16]	41
9	1 : 1.5	*t*BuXPhosAuCl (5 mol%), $NaBArF_{24}$ (7 mol%)[16]	59
10	1 : 1.5	BrettPhosAuNTf_2 (5 mol%)[19]	29
11	1 : 1.5	XPhosAu(NCMe)SbF_6 (5 mol%)[20]	49
12	1 : 1.5	Dichloro(2-picolinato)gold(III)[21]	0
13	1 : 1.5	IPrAuNTf_2[16]	23
14	1 : 1.5	IPrAuCl (5 mol%), $AgSbF_6$ (7 mol%)[22]	25
15[b]	1 : 1.5	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	65
16[c]	1 : 1.5	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	57
17	1.5 : 1	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	66
18	1 : 2	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	70
19	1 : 3	[JohnPhosAu(NCMe)]SbF_6 (5 mol%)	66
20	1 : 2	Me_3PAuCl (5 mol%), $AgSbF_6$ (10 mol%)	64

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[a] The yield for **12a** was determined via ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. The reaction was performed in 1,2-dichloroethane (DCE) at room temperature. If not stated otherwise, the concentration was 0.1 M for **1a**. [b]0.05 M for **1a**. [c]0.2 M for **1a**.

Raising the equivalents of **11a** to 1.5 increased the yield of **12a** which is why this ratio was initially kept for the further catalyst screening (entry 2). Starting from JohnPhos-type ligands, we first varied the counterion[23] as well as the other substituents attached to the phosphor atom of the phosphine (entries 3-6). The yields barely changed and were in the range of 56 to 67%. The usage of sterically more demanding phosphine ligands, like XPhos and BrettPhos, led to a strong decrease of the yield (entries 7-11). The usage of the gold(III) complex dichloro(2-pyridinecarboxylato)gold did not give any addition product at all (entry 12). When using *N*-heterocyclic carbene ligand[22] complexes with different counterions, the product was only formed in low yields (entry 13 and 14). Lowering the concentration of the starting materials resulted in no significant change of the yield; though the reaction time noticeably increased (entry 15). Increasing the concentration is accompanied by a decrease of the reaction yield (entry 16). A post-optimization of the ratio of **1a** and **11** (entries 17-19) showed that the ideal ratio of **1a** and **11** is 1:2 (entry 18, see Figure S7).

In the second part, we performed the reaction on a preparative scale (0.4 mmol) in order to evaluate the scope of the chloroalkynylation (Scheme 2) under the optimized reaction conditions (entry 18 in Table 1). The size of the alkyl chain of alkyne **11** has no significant impact on the yield (**12a** to **12c**). When the alkyne **11** bears a substituent at the *para* position of the aryl unit, the yield increases only with electron-donating substituents (**12d** to **12f**) which gave yields up to 90% (**12f**). In the case of electron-withdrawing substituents attached to the *para* position of the alkyne **11**, e.g. for **11e**, no selective formation of the corresponding enyne product could be observed. The substitution pattern (*para* vs. *ortho*) of the aromatic unit of the chloroarylacetylene is not important as the yields for **12g** and **12h** are almost the same. On the contrary, the electronic nature of the substituent attached to the aromatic unit of the chloroarylacetylene **1** is crucial: Chloroarylacetylenes **1** with electron-withdrawing substituents lead to high yields of the corresponding enynes **12**, whereas electron-donating groups decrease the yield (**12f** to **12j**). For chloroarylacetylenes with strong electron-donating groups, e.g. for chloroarylacetylene **1f**, an unselective reaction was observed that delivered the enyne product in significant lower yields (<20%).

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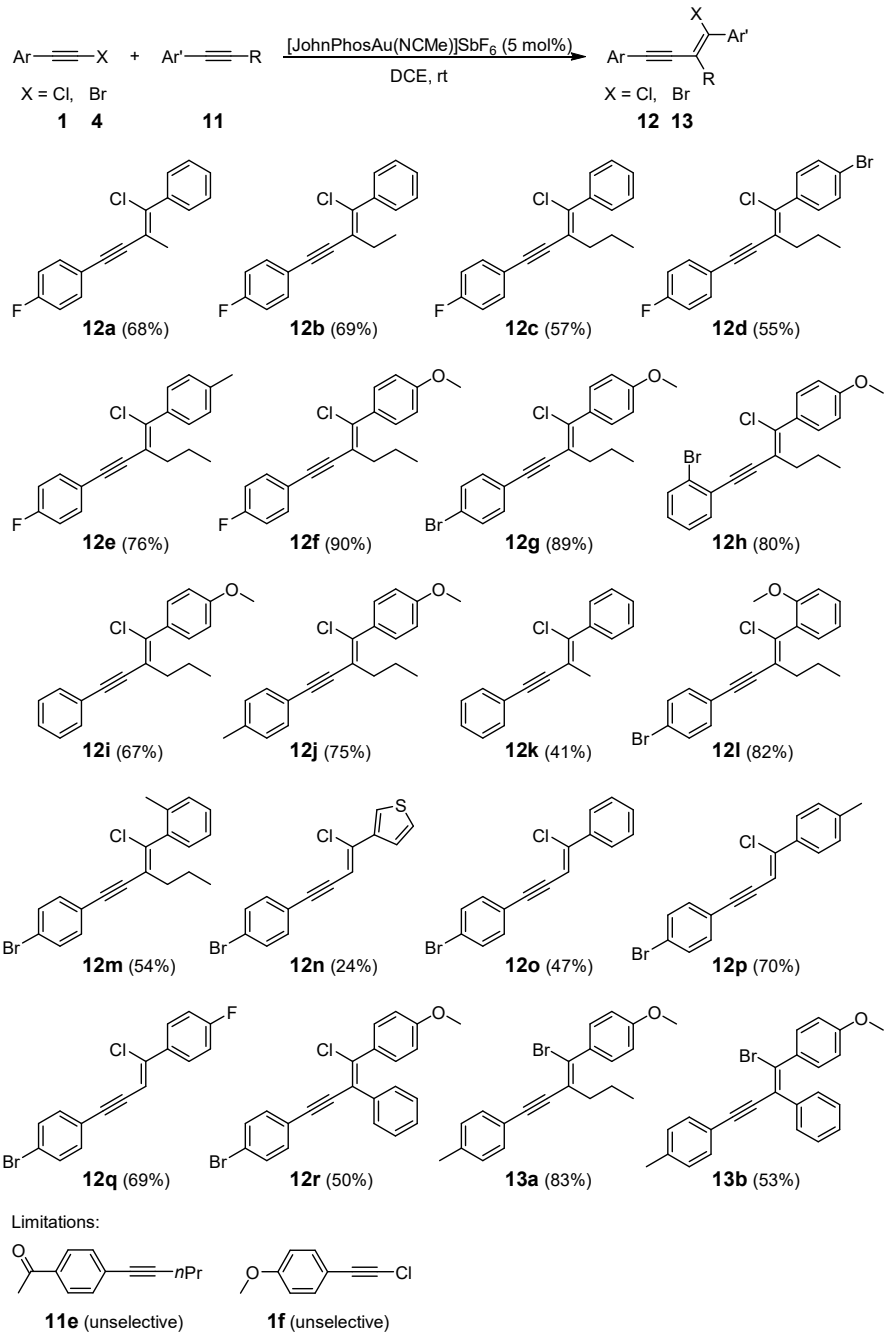

Scheme 2. Evaluation of the substrate scope of the gold(I)-catalyzed haloalkynylation of aryl alkynes **11**.

To our delight, the scope of the reaction could be extended to both terminal aryl alkynes and diaryl alkynes. Here again, only one regioisomer was obtained (**12n** to **12r**). Furthermore, the analogous reaction of bromoarylacetylenes (**4**) led to similar yields (**13a** and **13b**).

In the third step, we wanted to gain an insight into the reaction mechanism. As model reaction we have chosen the gold(I)-catalyzed reaction of phenylchloroacetylene with 1-phenyl-1-propyne (**11a**) employing both Me_3P and JohnPhos as ligands of the gold catalyst (Scheme 3). For the addition of the alkyne **11a** to the gold complex **14** two realistic reaction pathways were considered, namely the addition to the C2 (route *A*) or C1 position (route *B*)

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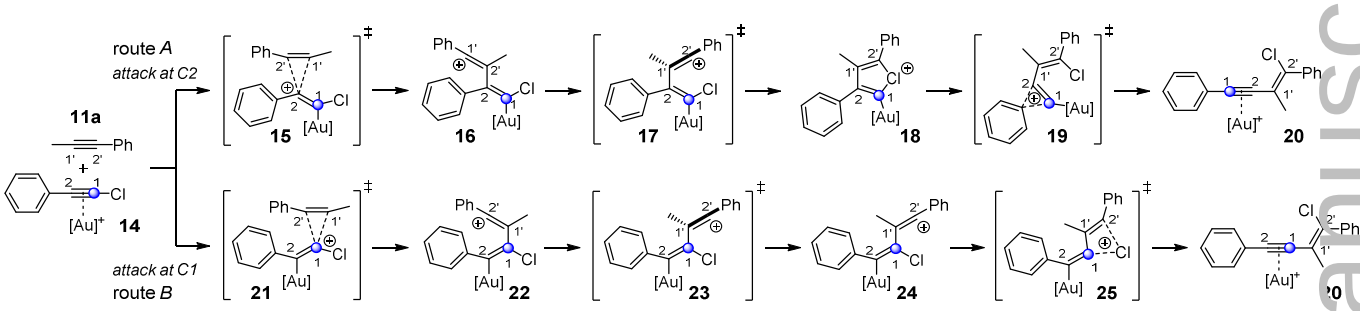
of the complex **14**. Both reaction pathways lead to the same product (**20**), which corresponds to the gold(I) complex of the successfully isolated enyne **12k** (Scheme 2). Route *A* starts with the addition to the carbon atom C2 of the gold complex **14** and proceeds via the vinyl cation **16** to the chloronium ion **18**. The subsequent shift of the aryl group leads to the gold complex **20** in which the carbon atom, that was initially attached to the chlorine atom, is now directly bound to the aromatic unit. A mechanism involving a bromonium cyclic intermediate similar to **18** has been proposed for the bromoalkynylation of 1,2-disubstituted alkenes.[8] Route *B* starts with the addition to the carbon atom C1 of the gold complex **14** forming the vinyl cation **22**. After rotation around the C1-C1' axis, the vinyl cation **24** is formed which can be stabilized via a 1,3-chlorine shift leading to complex **20**. The carbon atom, which was formerly attached to the chlorine atom, is now connected to the alkenyl unit.



Scheme 3. The gold(I)-catalyzed 1,2-chloroalkynylation of alkyne **11a** can proceed via an attack at both carbon atoms C2 (route *A*) and C1 (route *B*) of the alkyne complex **14**.

To examine through which of the previously discussed reaction pathways (route *A* and route *B*, Scheme 3) the haloalkynylation reaction proceeds, the reaction of alkyne **11a** with gold complex **14** was calculated by means of DFT methods (B3LYP[24], PBE0[26], M06-2X[27] and B97-D[28]) with dispersion corrections[25] and different basis sets (see Supporting Information). The calculated data are summarized in Tables S1 and S2 as well as Figures 1 and S13.

Let us consider the values obtained by B3LYP (B3LYP-D3BJ(dichloroethane as solvent)/B3//B3LYP-D3BJ/B1) with JohnPhos as ligand of the gold catalyst for both reaction pathways (route *A* and *B* in Scheme 3). It becomes obvious that in either case the rate-determining step is the first one, *i.e.* the addition of the alkyne **11a** to the complex **14** (Figure 1). With this level of theory, the activation barrier for route *A* amounts to 13.8 kcal/mol. The intermediate **16** (route *A*) can be stabilized through rotation around the C2-C2' single bond to form chloronium ion **18** (ΔG = -9.4 kcal/mol) (for numbering see Scheme 3). The activation barrier for the subsequent aryl shift exhibits a value of 9.1 kcal/mol. However, the activation barrier for the rate-determining step of route *B* amounts to 21.3 kcal/mol and is therefore significantly higher than that for route *A* (13.8 kcal/mol) (Figure 1). The thus formed vinyl cation **22** can now merge into the conformer **24** by rotation. In contrast to route *A*, the

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rotation leads to no stabilization (ΔG = +2.4 kcal/mol). The final step is the formation of gold complex **20** via a 1,3-chlorine shift which has a slightly lower activation barrier (5.4 kcal/mol) than the rearrangement of the aryl group for route *A* (9.1 kcal/mol) (Figure 1).

Also all other density functionals (PBE0, M06-2X and B97-D; Table S1) predict that route *A* is energetically favored compared to route *B.* Thus, all calculations forecast the preferred addition of the alkyne **11a** to the carbon atom C2 of **14** followed by a 1,2-aryl shift (route *B*, for numbering see Scheme 3).

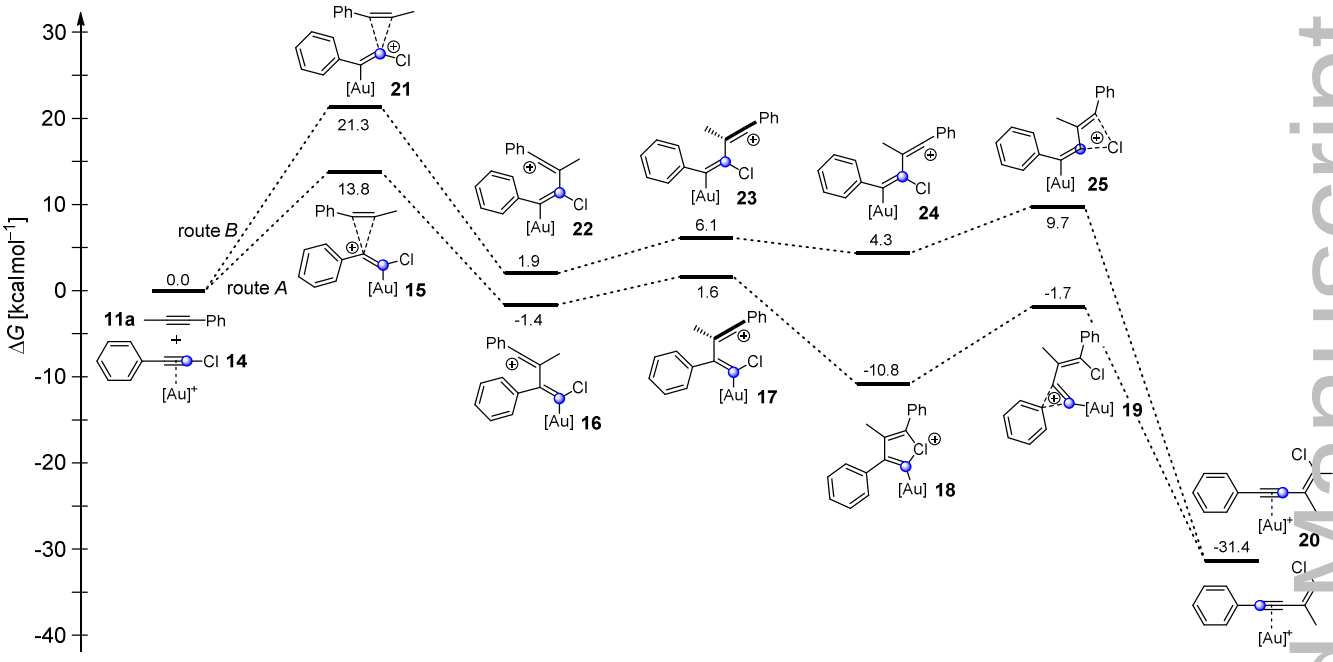
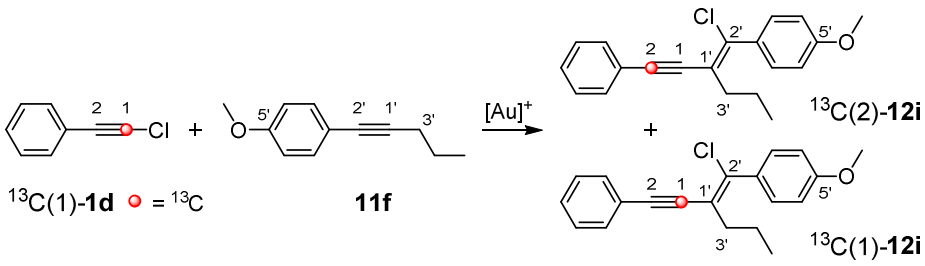


Figure 1. Free-energy (ΔG) profile for the gold(I)-catalyzed 1,2-haloalkynylation of alkyne **11a** via an attack at the carbon atom C2 (route *A*) and C1 (route *B*) of alkyne complex **14**, respectively, calculated by means of B3LYP-D3BJ(SMD)). $[Au]^+$ = JohnPhosAu$^+$.



Scheme 4. Investigation of the reaction mechanism of the gold(I)-catalyzed chloroalkynylation of **11f** by ^{13}C-labeled **1d**.

To verify our calculations, we attempted to confirm the previously proposed reaction mechanism. We assumed that ^{13}C-labelling of one of the starting materials should help gaining mechanistic insights. Therefore, we synthesized the chlorophenylacetylene in which

the outer acetylenic carbon atom is ^{13}C-labeled (^{13}C(1)-**1d**; Scheme 4). The gold(I)-catalyzed chloroalkynylation of the aryl alkyne **11f** delivered the enyne product ^{13}C-**12i** with a total yield of 81%. A closer look at the ^{13}C NMR spectrum reveals that the ^{13}C signals for both acetylenic carbon atoms C1 and C2 are enriched with the carbon isotope ^{13}C (Figures S14 and S15). According to the quantitative ^{13}C NMR spectrum, the percentage of ^{13}C is 14 and 98 times, respectively, higher at the positions C1 and C2 than that for the quaternary carbon atom C5' which just shows the natural abundance of the carbon isotope ^{13}C (~1%) (Figure S15). As both intensive signals of the acetylenic carbon atoms (C1 and C2) exhibit no splitting pattern (one would expect a doublet corresponding to the ^{1}J coupling of both ^{13}C-labeled acetylenic carbon atoms), the ^{13}C-enriched carbon atoms (C1 and C2) can not be present in the same molecule. Therefore, the isolated enyne must be a mixture of both compounds ^{13}C(2)-**12i** and ^{13}C(1)-**12i** (Scheme 4). The ratio of both compounds ^{13}C(2)-**12i** and ^{13}C(1)-**12i** is determined via the integrals for the ^{13}C-enriched signals of C2 and C1, respectively, and amounts to 87:13 (Figure S15). This proves that the reaction proceeds via both reaction pathways (route *A* and *B* in Figure 1), whereby the pathway via the chloronium ion **18** (route *A*) is favored.

In conclusion, we have developed a gold(I)-catalyzed variant of the haloalkynylation reaction that gives direct access to conjugated and halogenated enynes with good to very good yields (up to 90%) from readily available starting materials while tolerating a broad substrate scope of both alkyne reactants. As the halogen pattern on both aromatic and vinylic unit allows for potential further transformations (see Scheme S1), the gold(I)-catalyzed haloalkynylation of aryl alkynes represents an attractive method for the synthesis of more complex conjugated systems. Of particular interest is the fact, that the enyne product can be formed through two complementary pathways: The regioselectivity of the C-C bond formation plays absolutely no role as rearrangement of the skeleton results in the same product. ^{13}C-labeling experiments prove that the reaction passes indeed through both ways. This interplay can be employed for the development of future novel carbon-carbon bond forming reactions.

Conflict of interest

There is no conflict of interest to declare.

Keywords

C-C bond forming reactions; DFT calculations; Enynes; Gold catalysis; Vinyl cations

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