Gold Catalysis

Dual Gold-Catalyzed Head-to-Tail Coupling of Iodoalkynes

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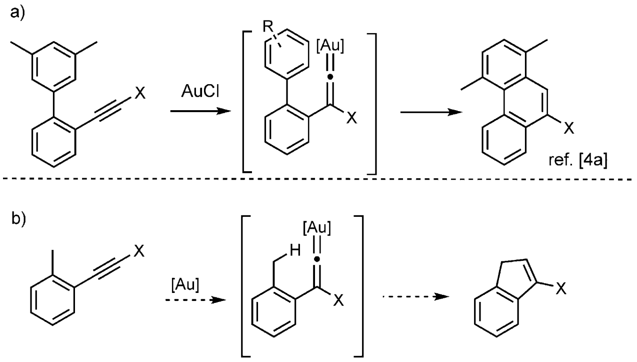
Abstract: Various haloalkynes are converted in the presence of a dual activation gold catalyst. Via a dual activation process a completely atom economic head-to-tail coupling delivers *gem*-dihalogenated conjugated enynes as valuable building blocks for organic synthesis.

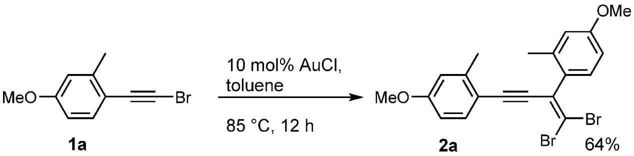
Reactive intermediates that enable strategies for a diverse set of downstream transformations play an important role for the ongoing success of homogeneous gold catalysis.[1] Recently, gold vinylidenes, resulting from the cyclization of diynes by dual catalysis[2] or by the reaction of gold acetylides with appropriate leaving groups,[3] allowed the design of various synthetically useful transformations. Furthermore, gold vinylidenes derived from a 1,2-iodo migration from iodoalkynes have also been discussed in several contributions.[4]

Inspired by a gold-catalyzed synthesis of phenanthrenes through a formal CH insertion of aryl CH bonds at a gold vinylidene (Scheme 1 a)[2a] and by the observed high reactivity for diyne-derived vinylidenes (even CH insertions of unactivated sp^3-CH bonds are possible), we assumed that a CH insertion of a benzylic CH bond into a gold vinylidene derived by a 1,2-halogen migration might also be feasible (Scheme 1 b). However, to our surprise, a completely different pathway, namely a head-to-tail dimerization of haloalkynes to synthetically valuable *gem*-dihalogenated enyne systems, was observed. To our knowledge, this reaction is to date unprecedented; most probably this originates from the fact that other transition metals are prone to redox chemistry that initiate different types of reactivity.[5] Our study on this new type of intermolecular dual gold-catalyzed process is discussed herein.

As an initial test reaction, the bromoalkyne **1 a** was converted under Fürstner's conditions for 12 h in toluene (Scheme 2).



Scheme 1. a) Fürstner's phenanthrene synthesis; b) planned CH insertion of benzylic CH groups.



Scheme 2. Initial observation of a head-to-tail dimerization of bromoalkyne **1 a**.

Complete consumption of the starting material took place, but no CH insertion or 1,2-halogen migration was observed. Instead, the *gem*-dibrominated enyne **2 a**, resulting from an unexpected head-to-tail alkyne dimerization of the starting bromoalkyne, was isolated in 64 % yield.[6]

Considering the structure of the product formed, we assumed that a gold acetylide should be one of the intermediates of the reaction. This assumption was based on our recent findings where we could demonstrate that gold acetylides can be formed via ligand exchange from organogold(I) species and haloalkynes. This process enabled the utilization of iodoalkynes as starting materials for dual gold-catalyzed reactions with diyne starting materials.[7] A head-to-tale dimerization of terminal alkynes has recently been reported by the Zhang group,[8j] and we could further demonstrate that σ,π-dinuclear propyne–gold acetylides (DAC = dual-activation catalysts) led to a better efficiency of this reaction.[9] As a consequence, we considered DAC catalysts or mixtures of organogold compounds with cationic gold species for the dimerization of haloalkynes as well. Indeed, a significant improvement was possible by using DAC **3 a** and an isolated yield of 72 % of **2 a** was obtained (Scheme 3). It is noteworthy that even chloroalkyne **1 b** could be dimerized in moderate yield under the same conditions.

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[+] Crystallographic investigation

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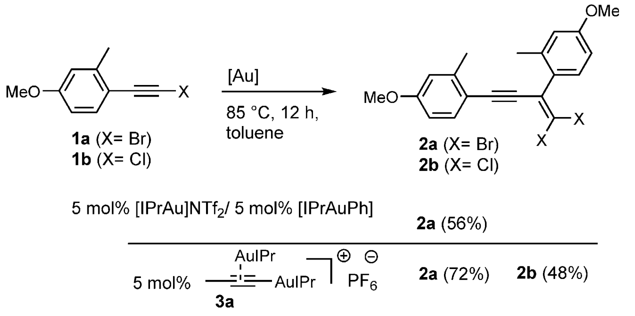
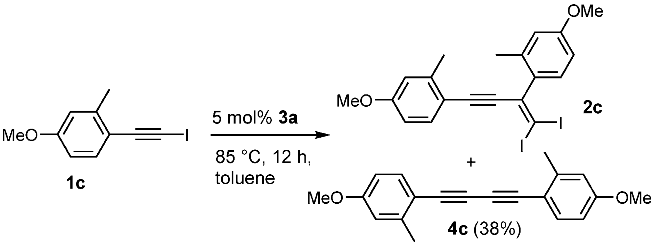


Scheme 3. Transformation of haloalkynes with dual-activation catalysts.



Scheme 4. Conversion of iodoalkyne **1c**.

A different scenario was observed with the iodoalkyne test substrate **1c** (Scheme 4). Its conversion delivered a mixture of different products. Among them, the desired product **2c** was obtained, but it could not be separated from several byproducts with the same polarity. The only separable compound was a tail-to-tail dimerization product **4c** in 38% yield. The structure of the obtained symmetric dialkyne was further verified by the results of an X-ray single crystal structure analysis (Figure 1).[10]

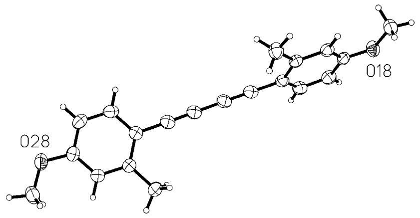
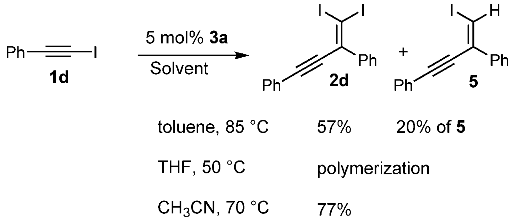


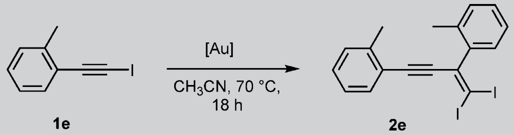
Figure 1. Solid-state molecular structure of **4**. Thermal ellipsoids are drawn at 50% probability level.

To optimize the iodoalkyne dimerization, simple iodophenylacetylene was converted using different solvents. For this system no head-to-head dimerization was observed; instead, in toluene, mono-iodinated enyne **5** was obtained as an inseparable by-product in 20% yield (Scheme 5). Although in THF only polymerization took place, acetonitrile turned out to be a suitable solvent for a selective dimerization. In this case, less than 1% yield of the mono-iodo compound **5** was obtained (77% yield of **2d**).



Scheme 5. Solvent optimization.

Table 1. Catalyst optimization.

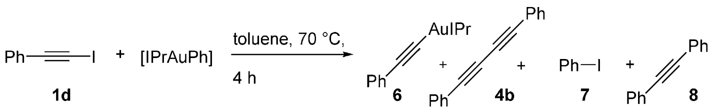


Entry	Catalyst	Yield [%]
1	DAC–PF_6 **3a** (5 mol%)	40
2	DAC–SbF_6 **3b** (5 mol%)	40
3	DAC–OTs **3c** (5 mol%)	52
4	DAC–NTf_2 **3d** (5 mol%)	52
5	DAC–OTf **3e** (5 mol%)	47
6	DAC–BF_4 **3f** (5 mol%)	45
7	$AuCl_3$ (10 mol%)	12
8[a]	AuCl (20 mol%)	10
9	[IPrAu]NTf_2 (10 mol%)	14
10	[IPrAuPh] (10 mol%)	0.5
11	[IPrAu–propinyl] (10 mol%)	–

a) reaction in toluene, 20 h, 80 °C.

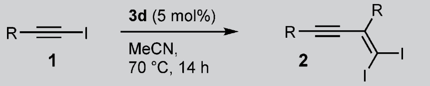
Lower yields were obtained with substrate **1e** bearing a methyl group in the *ortho* position of the aromatic moiety. As a consequence, we performed an additional catalyst screening in acetonitrile as solvent (Table 1). In a first series of experiments, different counter anions for the dual-activation catalysts **3** were applied. Indeed, a moderate counter anion effect was observed and $[NTf_2]^-$ and $[OTs]^-$ turned out to be most efficient (Table 1, entries 1–6). $AuCl_3$ and AuCl were not suitable for this system (Table 1, entries 7 and 8), as was the case for [IPrAu]NTf_2 (entry 9). Test reactions with organogold species in the absence of a cationic gold species showed no conversion (Table 1, entries 10 and 11).

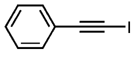
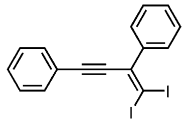
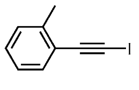
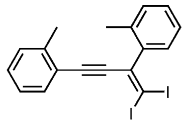
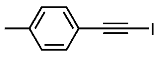
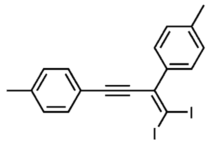
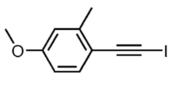
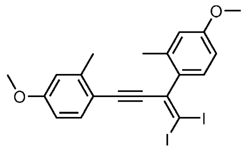
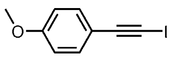
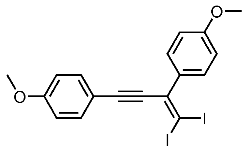
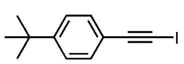
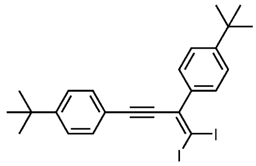
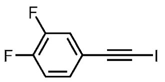
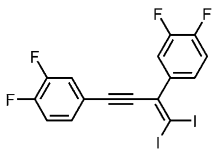
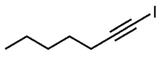
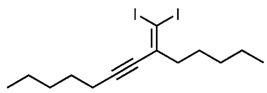
Under the optimized conditions, various iodoalkynes were converted in order to evaluate the scope of the transformation. With simple iodophenylacetylene, the corresponding enyne could be obtained in 80% yield (Table 2, entry 1). The lower yield for starting material **1e** (52%; Table 2, entry 2) might be due to the steric bulk of the methyl group in the *ortho* position. This conclusion comes from the conversion of the corre-



Scheme 6. Stoichiometric reaction with [IPrAuPh].

Table 2. Substrate scope.

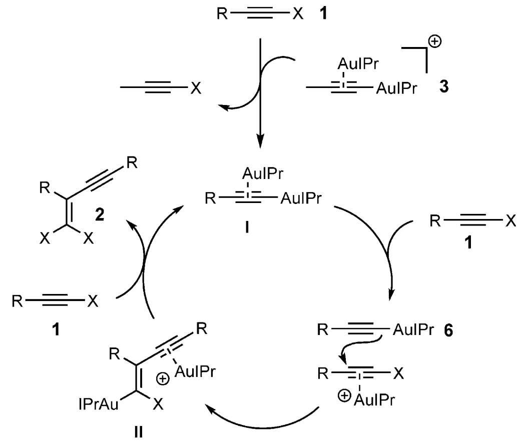


Entry	1	2 (yield [%])
1	 **1d**	 **2d** (80%)
2	 **1e**	 **2e** (52%)
3	 **1f**	 **2f** (80%)
4	 **1c**	 **2c** (51%)
5	 **1g**	 **2g** (74%)
6	 **1h**	 **2h** (79%)
7	 **1i**	 **2i** (75%)
8	 **1j**	 **2j** (55%)

sponding starting material **1 f** bearing the methyl group in the *para* position of the aromatic system, which should be electronically comparable. Therefore the higher yield of 80% must result from decreased steric shielding (Table 2, entry 3). The same effect was observed for substrates **1 g** and **1 h** (Table 2, entries 4 and 5). A *tert*-butyl substituent in the *para* position was also well tolerated (Table 2, entry 6). Difluoro-substituted electron-deficient substrate **1 i** smoothly delivered the corresponding enyne **2 i** in good yield (Table 2, entry 7). Next we considered aliphatic iodoalkynes as starting materials as well. Indeed with iodohexyne **1 j** the desired product was obtained, but yields were only moderate (Table 2, entry 8).

To gain further insights about the initiation and the catalyst transfer step, iodophenylacetylene **1 d** was converted in the presence of stoichiometric amounts of [IPrAuPh] (Scheme 6). Indeed, the formation of the expected gold acetylide **6** could be detected by ^{1}H NMR spectroscopy. Analyzing the mixture by GC-MS revealed that, besides the expected iodobenzene (that should result from a catalyst transfer, a thermodynamically driven halogen–metal exchange of both starting materials to provide **6** and **7**), a head-to-head dimerization also took place. In addition, even diphenylacetylene as cross-coupling product was detected in significant amounts, an evidence for a possible additional redox catalytic cycle that might be in operation.[11]

Based on this finding and analogies to the synthesis of iodofulvenes,[7] we postulate the mechanism that is depicted in Scheme 7. The initiating step would be a transfer of the two {IPrAu} fragments by the dual-activation catalyst.[9] In the next step, the cationic gold species activates the triple bond of another iodoalkyne, which is then attacked by the σ-activated gold acetylide. This intermolecular dual-catalyzed reaction delivers vinyl gold species **II**. Finally, catalyst transfer onto a new substrate molecule releases the product and regenerates a gold acetylide. In this step, a competing protodemetalation can explain the formation of monoiodinated alkenes as byproducts. The mechanism of the catalyst transfer onto iodoalkynes remains unclear, but stoichiometric experiments, as well as the formation of significant amounts of Glaser-type head-to-head products in some reactions hint that a possible



Scheme 7. Mechanistic proposal.

oxidative addition of iodoalkynes at the gold(I) species might participate in this step.

In conclusion, we have shown that, in the presence of a dual-activation catalyst, haloalkynes can be dimerized in a head-to-tail fashion. This completely atom-economic reaction demonstrates that iodoalkynes can even serve as substrates for dual catalyzed reactions in an intermolecular fashion. From easily accessible iodoalkynes, *gem*-dihalogenated enynes, valuable building blocks in organic synthesis, can be obtained.

Keywords: alkenes · alkynes · dual activation · gold · halogenated compounds

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[10] CCDC 1030440(**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Both products of C–C bond formation (**4a** and **8**) can be explained by oxidative addition of **1d** to both organometallic species present during the transformation ([IPrAuPh] and **6**) and subsequent reductive elimination connecting the two organic groups (for the C–C bond formation after reductive elimination at gold, compare: a) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592 – 597; b) A. S. K. Hashmi, T. D. Ramamurthi, M. H. Todd, A. S.-K. Tsang, K. Graf, *Aust. J. Chem.* **2010**, *63*, 1619 – 1626).

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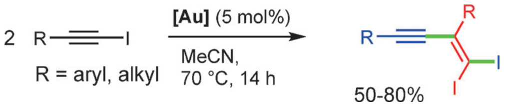
COMMUNICATION



Various haloalkynes are converted in the presence of a dual-activation gold catalyst. Through a dual activation process, a completely atom-economic head-to-tail coupling delivers *gem*-dihalogenated conjugated enynes as valuable building blocks for organic synthesis.

Gold Catalysis

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Dual Gold-Catalyzed Head-to-Tail Coupling of Iodoalkynes