Catalysis |*Hot Paper*|

Synthesis of Fulvene Vinyl Ethers by Gold Catalysis

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Abstract: Gold-catalyzed cyclization of 1,5-diynes with ketones as reagents and solvent provides diversely substituted vinyl ethers under mild conditions. The regioselectivity of such gold-catalyzed cyclizations is usually controlled by the scaffold of the diyne. Herein, we report the first solvent-controlled switching of regioselectivity from a 6-*endo-dig*- to 5-*endo-dig*-cyclization in these transformations, providing fulvene derivatives. With respect to the functional-group tolerance, aryl fluorides, chlorides, bromides, and ethers are tolerated. Furthermore, the mechanism and selectivity are put to scrutiny by experimental studies and a thermodynamic analysis of the product. Additionally, 6-(vinyloxy)fulvenes are a hitherto unknown class of compounds. Their reactivity is briefly evaluated, to give insights into their potential applications.

Introduction

Starting with the discovery of the gold-mediated dual activation[1–3] of 1,5-diynes possessing at least one terminal alkyne by Zhang et al.[4] and Hashmi et al.,[5] our group has developed a long standing interest in the chemistry of 1,5-diynes.[3,6] This seemingly simple scaffold has opened up a rich chemistry in synergy with gold, triggered by highly reactive organogold intermediates. The nucleophilic attack of a gold acetylide onto another alkyne, π-coordinated by gold, leads to aurated gold vinylidene[4–8] or diaurated phenyl cation[9–11] intermediates, respectively. These highly electrophilic species enable new synthetic methods.[3] Recently, our group reported the activation of 1,5-diynes by only one single gold center. In dependency of the substitution pattern of the substrate, either aurated vinyl cations[12] or aurated aryl cations[13] are the key intermediates (Figure 1). In all cases the regioselectivity of the cyclization is controlled by the substitution pattern of the 1,5-diyne. These high energy species can be utilized for the development of new transformations, yet the reactivity provides a challenge regarding selectivity.

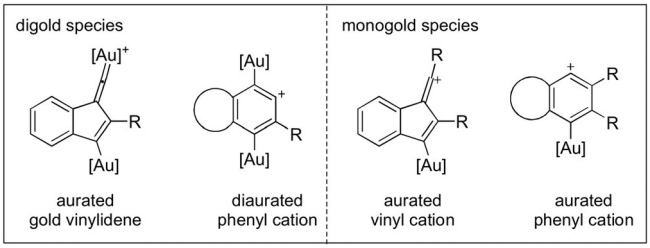

Figure 1. Proposed intermediates of gold-catalyzed 1,5 diyne cycliations.

Vinyl ethers are a highly relevant moiety for organic synthesis, allowing a rich follow-up chemistry.[14] They are used in many fields, especially the impact on polymer science is noteworthy.[15] As a scaffold of interest, many protocols for vinyl ether synthesis have been developed.[16] Hydroalkoxylation of alkynes has been a central access to vinyl ethers, with Reppe being the pioneer of that field.[17] Many carbophilic metals catalyze this interesting transformation, such as mercury,[18] silver[19] and ruthenium[20] to name but a few, yet often harsh conditions or elaborate starting materials are necessary. Utimoto and later Teles et al. showed that gold salts also catalyze the attack of alcohols on alkynes, but often in favor of giving ketal or ketone products via double addition.[21] A gold(I)-catalyzed

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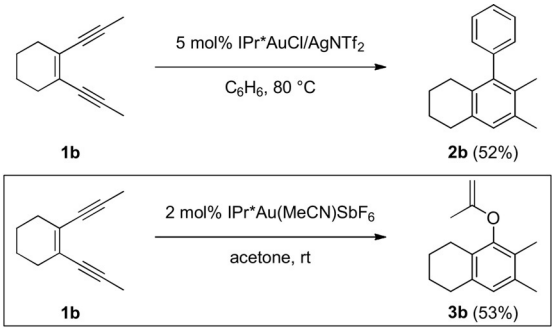
approach by Corma et al. gave convenient conditions for vinyl ethers, but is limited to electron-poor alkynes.[22] Other gold-mediated methods have been introduced, giving mild synthetic strategies.[23] The mechanism of this useful transformation has been thoroughly investigated.[24] In 2013 Shi et al. substituted alcohols for cyclic 1,3-diketones allowing clean conversion to vinyl ethers via the attack of oxygen. However, noncyclic 1,3-ketones already failed to give the desired oxygen addition.[25]

We envisioned a vinyl ether synthesis accessible by simple starting materials under mild conditions by exploiting the aforementioned aurated carbocationic intermediates instead of alkynes as electrophiles and simple ketones instead of alcohols or 1,3-ketones as nucleophiles. Due to the high reactivity of these species a kinetic control of the reaction should be feasible preferring the attack of the carbonyl oxygen instead of the enol carbon of the respective tautomer, which is only available in very low concentrations in the reaction mixture. After elimination of a proton, the vinyl functionality is formed by the former ketone. Such a method would be complementary to the briefly introduced established methods for vinyl ether preparation.

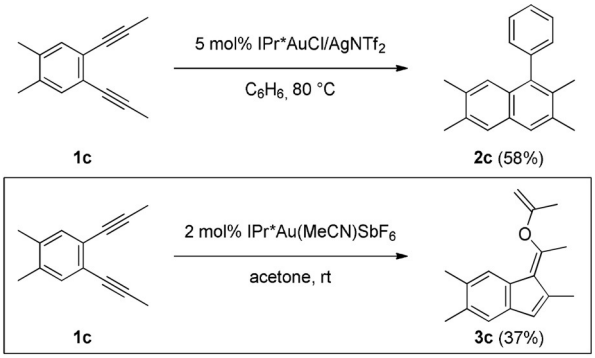
Results and Discussion

In order to develop this methodology, we started the investigations with substrate **1b** which was, in analogy to our previous work,[13] supposed to act as a precursor for an aurated phenyl cation intermediate. However, the previously reported intramolecular trapping pathways are suppressed by the attached short side chains. Whether trapping the postulated intermediate intermolecularly is possible, was tested using benzene as solvent giving **2b**. Next, acetone as a symmetric and common reagent was tested as solvent. To our delight, by using acetone as solvent and 2 mol% IPr*Au(MeCN)SbF_6 as catalyst a full conversion was observed yielding the desired product **3b** in moderate yield after 4 h at rt (Scheme 1).

We moved on to the analogous 1,5-diyne with an aromatic backbone **1c**. Methyl groups on the backbone were chosen to ease investigation by ^{1}H NMR spectroscopy. Remarkably, we observed that the cyclization mode of this specific substrate can be altered by the applied solvent/nucleophile. A conducted test reaction in benzene gave a clean conversion to the respective naphthalene derivate **2c**. In acetone however the selectivity is switched from a *6-endo-dig* to a *5-endo-dig* cyclization, as confirmed by ^{1}H,^{1}H NOESY experiments. This influence of a solvent on the gold-mediated reactions of 1,5-diynes is unprecedented to the best of our knowledge (Scheme 2).



Scheme 1. Gold-catalyzed cyclization of **1b** in benzene and acetone, respectively.



Scheme 2. Gold-catalyzed cyclization of **1c** in benzene and acetone, respectively.

Optimization experiments to improve the efficiency of the reaction, with **1c** as substrate, were conducted. As gold salts as π-acids[26] might also catalyze the hydrolysis of the products in the presence of water, the reagent grade acetone stored under air was substituted by dry acetone.[27] However, the yield only improved by a narrow margin up to 41%. Adding 4 Å molecular sieve to the reaction led to decomposition and an incomplete conversion of the starting material. An optimized work up with deactivated silica by using a mixture of PE and NEt_3 instead of PE and EA gave a significant improvement, with 67% of **3c** being isolated.

Furthermore, we conducted a small catalyst screening (Table 1) testing bulky carbenes and a phosphine as ligands (Figure 2). A few counter ions, too, were considered.

Table 1. Catalyst and counter ion screening in dry acetone under air, with 2 mol% catalyst loading and a concentration of 150 μmol mL^{-1} **1c**. All yields are isolated yields.

Entry	Catalyst	Reaction time	Yield **3c**
1	IPr*Au(MeCN)SbF_6	3 h	67%
2	Me_4^{t}BuXPhosAu(MeCN)SbF_6	4 d	32%
3	IPrAu(MeCN)SbF_6	5 h	39%
4	Me_2CAACAuCl/AgSbF_6[a]	1 d	24%
5	IPr*AuCl/AgSbF_6[b]	3 h	decomposition
6	IPr*AuCl/NaBArF[b]	2 d[c]	no conversion
7	IPr*AuCl/NaBArF[a]	1 d	22%
8	IPr*AuNTf_2	3 h	34%
9	AgSbF_6	2 d[c]	no conversion

[a] The chloro gold complex and chloride scavenger were dissolved in a 2:1 DCM:MeCN mixture and stirred at rt for 20 min. The solvent was removed in vacuo and the residue suspended in DCM. This suspension was filtered over a thin plug of silica, the solvent removed again and **1c** dissolved in acetone added to the residue. [b] The chloro gold complex was dissolved with **1c** in acetone, then the chloride scavenger was added. [c] After one day the reaction was heated to 60 °C for another day.

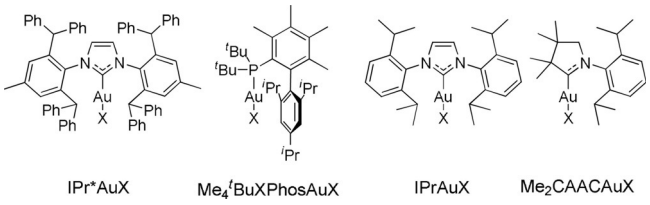


Figure 2. Complexes used in the catalyst screening.

The initial test system of IPr*Au(MeCN)SbF_6 proved to be superior over all tested conditions. The screening revealed that albeit silver salts do not consume the starting material, the presence of silver in the gold catalysis leads to decomposition.

With an acceptable yield we moved on to explore if the transformation can be applied on a broad scope of 1,5-diyne systems (Table 2).

Eleven substrates were tested, of which only the olefinic backbone, entry 2, and thiophene backbone, entry 11, gave vinyloxy arenes. These results are in good agreement with already established reactivities.[13,10] The terminal diyne **1a** showed only slow decomposition under the reaction conditions. Very electron-rich and very electron-poor substrates **1d**, **1e** and **1k** gave no reaction at rt and decomposed slowly upon heating. Presumably, the products react unselectively at higher temperatures in the presence of gold salts. Five substrates gave 6-(vinyloxy)fulvenes in moderate to good yields, including a larger π-system, entry 9, and halogenated compounds, entry 6 and 7. Crystals suitable for X-ray single crystal structure analysis were gained by crystallization of **3j** from DCM and pentane at 4 °C, confirming the compound and its geometry (Figure 3).[28]

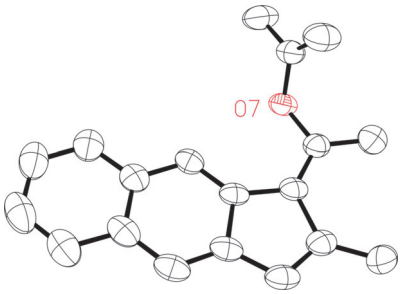
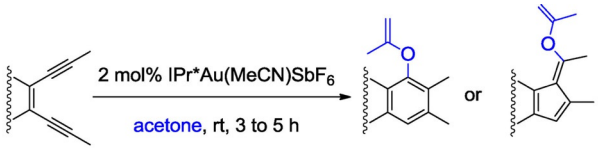


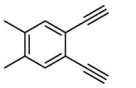
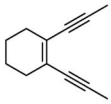
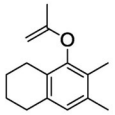
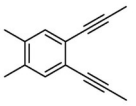
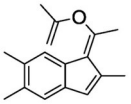
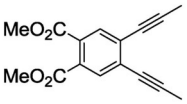
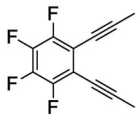
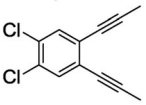
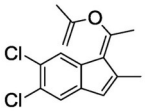
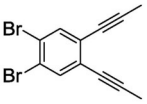
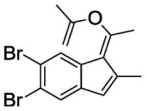
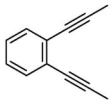
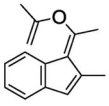
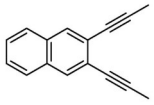
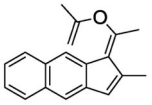
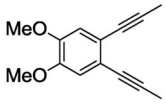
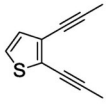
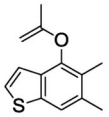
Figure 3. Molecular structure of **3j** in the crystal. Hydrogen atoms were omitted for clarity.[28]

Presuming that aurated vinyl[12] or aryl[13] cations are formed initially, which then are attacked by the solvent, substituents larger than methyl on the alkynes of the substrates would be prone to compete with acetone for the cationic intermediate. To put the competition of intra- vs. intermolecular attack up to scrutiny we expanded the scope of test substrates (Table 3).

Interesting enough, for the phenyl-substituted 1,5-diyne, entry 1, the intramolecular attack of the vinyl cation intermediate at the aromatic ring only occurs to a minor extend, product **4m** was obtained in 6%. Instead, acetone attacks efficiently, giving the 6-(vinyloxy)fulvene **3m** in 69% yield. Entry 2 shows that a deactivation of the aromatic system selectively leads to the vinyl ether **3n**, whereas electron-rich arenes give a mixture of both products (entry 5). The electron-poor system

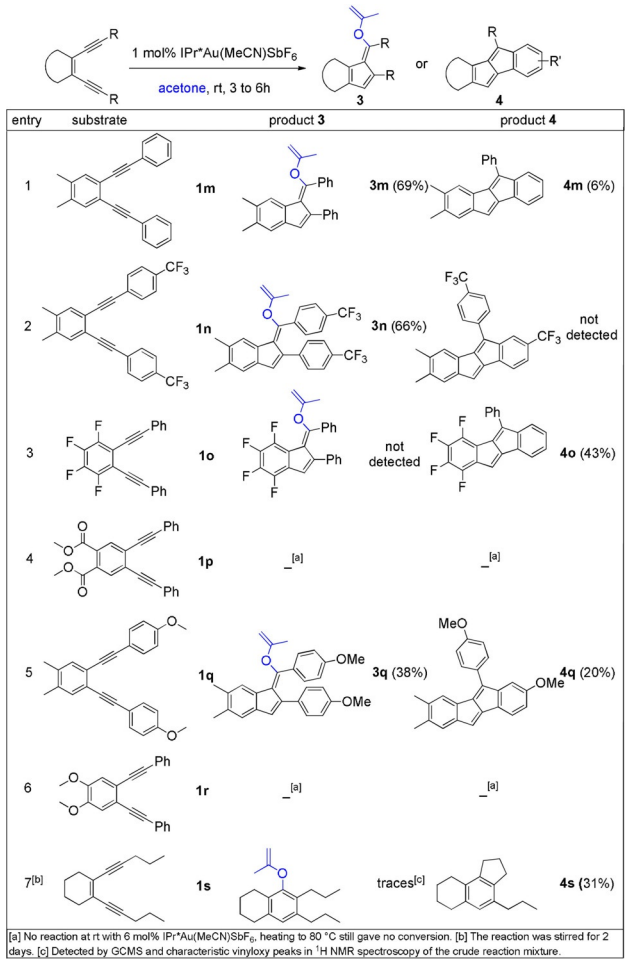
Table 2. Exploration of scope and limitations. Reactions were carried out with dry acetone under air and at a concentration of 150 μmol mL^{-1} substrate.



entr	starting material		product	
1		**1a**		[a]
2		**1b**		**3b** (53%)[b]
3		**1c**		**3c** (67%)
4		**1d**		[a]
5		**1e**		[a]
6		**1f**		**3f** (78%)
7		**1g**		**3g** (75%)
8		**1h**		**3h** (32%)
9		**1j**		**3j** (47%)
10		**1k**		[a],[c]
11		**1l**		**3l** (57%)

[a] No reaction at rt with 6 mol% IPr*Au(MeCN)SbF_6, heating up to 60 °C led to decomposition. [b] After 3 h reaction control by TLC showed mixture of product and starting material, another 2 mol% catalyst were added. [c] Additionally tested with 6 mol% Me_4tBuXPhosAu(MeCN)SbF_6 at 60 °C. Again no reaction at rt and decomposition at 60 °C.

Table 3. Intra- and intermolecular reaction of the intermediate. Reactions were carried out with dry acetone under air and a concentration of 150 µmol mL^{-1} substrate.



[a] No reaction at rt with 6 mol% IPr*Au(MeCN)SbF$_6$, heating to 80 °C still gave no conversion. [b] The reaction was stirred for 2 days. [c] Detected by GCMS and characteristic vinyloxy peaks in ^{1}H NMR spectroscopy of the crude reaction mixture.

in entry 3 provides only the dibenzopentalene product **4 o**. Presumably, the electron-withdrawing inductive effect of fluorine on the backbone destabilizes the vinyl cation intermediate via the σ-skeleton, inducing a faster intramolecular attack at the phenyl substituent. Very electron-rich and very electron-poor backbones (entry 4 and 6) gave no conversion at rt and decomposition at higher temperatures. The olefinic backbone with alkyl chains only gave the known[13] intermolecular C,H-insertion product **4 s** (entry 7).

Here too, the structure was confirmed by X-ray single crystal structure analysis. Suitable crystals were obtained by crystallization of **3 n** from DCM and pentane at 4 °C, confirming the compound and its geometry (Figure 4).[28]

Different solvents with carbonyl functionality were also tested (Table 4). Aldehydes do form the desired product, but the reaction is far less selective than with ketone nucleophiles. The product could not be separated from a mixture of unidentified compounds. Hence, the yield could not be determined. Cyclic ketones reacted well, except cyclobutanone (entry 2), possibly due to the build-up of ring strain upon forming a cyclobutenol moiety,[29] inhibiting the deprotonation of the oxonium intermediate. In case of unsymmetric ketones, the formation of the vinyloxy group obeys Hofmann's rule, giving the kinetic product **3 v** (entry 6). This indicates that in the deprotonation step to form the vinyl moiety, a sterically hindered base is involved, possibly the solvent itself or the aurated vinyl ether (in the protodeauration). When methanol was tested as solvent, a two-fold addition of solvent took place, the observed 5-*endo-dig* product **5** indicates that the polarity of the solvent influences the reaction pathway. Crystals of **5**, suitable for X-ray single crystal structure analysis, were grown from a hot pentane solution, which was cooled to −32 °C (Figure 5).[28]

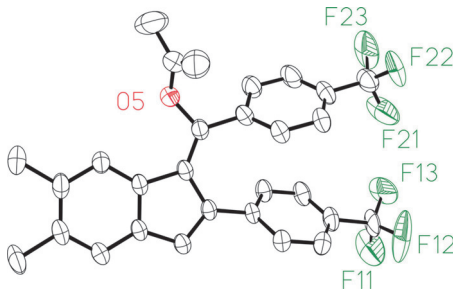


Figure 4. Solid state molecular structure of **3 n**. Hydrogen atoms were omitted for clarity.[28]

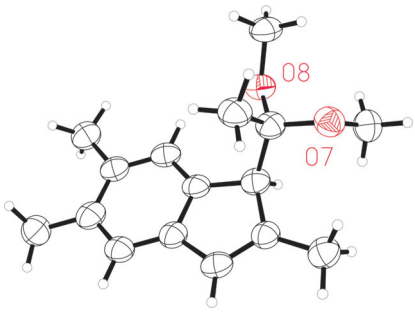
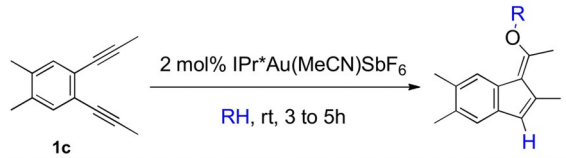


Figure 5. Solid state molecular structure of **5**.[28]

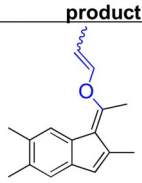
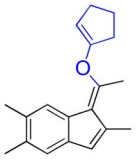
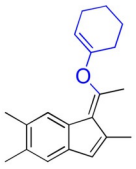
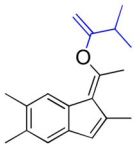
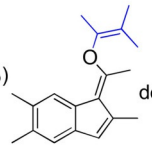
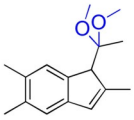
We assume that the mechanism for the different cyclizations follows principles discussed before (Scheme 3).[12,13] After π-coordination of the gold cation to one alkyne unit,[30] the other alkyne can attack it via its α- or β-carbon to form the two intermediates **IIa** and **IIb**, respectively. The formation of the benzoid aromatic system is a considerable driving force, resulting in the formation of the aurated phenyl cation **IIa**. The aromatic backbone on the other hand ends up forming a benzofulvene system. Why the cyclization mode for substrate **1 h** is switched from benzene to acetone could not be answered yet.

Apparently, the more polar environment tends to stabilize the aurated vinyl cation **IIb** over the respective aurated aryl cation. This could mean that the aryl cation is a transition state and not a true intermediate for this class of compounds.[13] It can be speculated that a transition state would not benefit as much as a vinyl cation intermediate from a carbocation stabilizing polar environment. DFT calculations regarding the influence of solvent on the intermediates were inconclusive.[31]

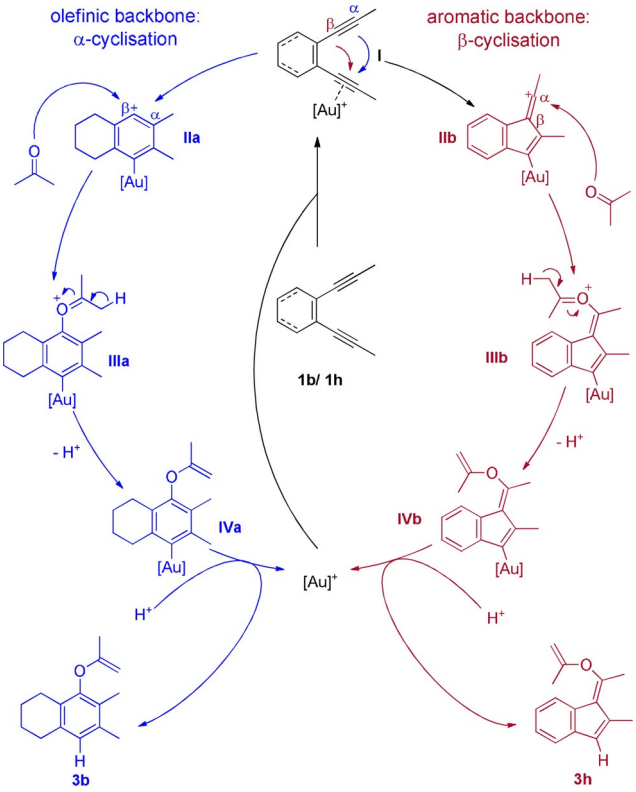
Table 4. Exploration of scope and limitations. Reactions were carried out with dry acetone under air and at a concentration of 150 µmol mL^{-1} substrate.



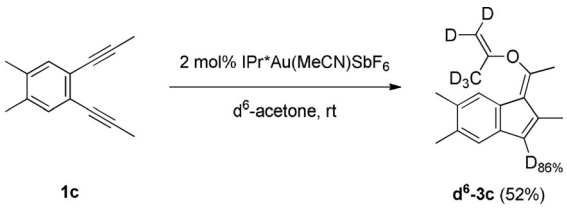
1c

entry	RH	product
1		 detected, but not isolated[a]
2		– [b]
3		 **3t** (52%)
4		 **3u** (45%)
5		– [c]
6		 **3v** (34%)  not detected
7		– [c]
8		 **5** (58%)

[a] Detected *via* GCMS und ^{1}H NMR spectroscopy, but could not be isolated. No yield determined [b] No conversion with 6 mol% IPr*Au(MeCN)SbF$_6$ at 50 °C. [c] Decomposition.



Scheme 3. Proposed mechanism for the gold-catalyzed formation of **3 b** and **3 h**.



1c

d^6-3c (52%)

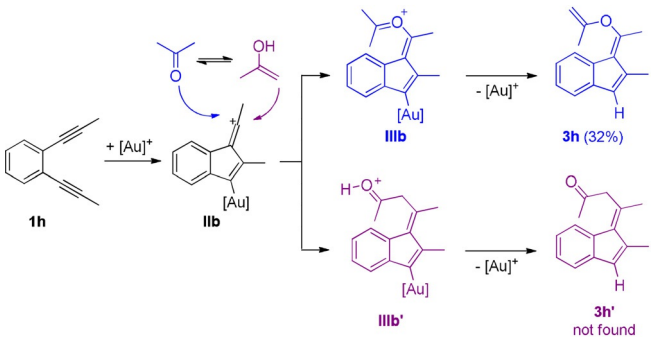
Scheme 4. Deuteration experiment. The rate of deuteration was determined by ^{1}H NMR spectroscopy of the product **d^6-3 c**.

Either way, these highly electrophilic species are attacked by the carbonyl oxygen of the solvent. The resulting aurated oxonium ions **IIIa** and **IIIb** can then eliminate a proton to form the aurated vinyl ethers **IV**. Protodeauration in turn releases the respective products **3 b** and **3 h** and releases the gold cation back into the catalytic cycles. To confirm intermediate **IVb**, the substrate **1 c** was left to react in deuterated acetone (Scheme 4). An additional deuteration experiment using normal acetone and 5% D_2O failed, as the increased water content let to decomposition.

To test whether the selectivity of the cyclization mode can be „switched" by changing the polarity of the reaction medium, 10 equiv. of acetone were added to **1 c** dissolved in benzene and left to react in presence of 2 mol% IPr*Au(MeCN)SbF$_6$. However, even after several days, only trace amounts of benzene addition product **2 c** and no acetone adducts were observed by GCMS. An experiment using an acetone/benzene mixture 1/3 gave small amounts of **3 c** and about 10 to 20% of **2 c** at low conversion after 16 h, as confirmed by GCMS and crude ^{1}H NMR spectra. Reliable yields were not determined from the crude mixture, but no isomers of **3 c** or **2 c** were detected.

Acetone acting as an *O*-nucleophile is unusual. In the beginning of our studies, we postulated that the high reactivity of the electrophilic intermediate should be able to enforce a kinetic control. I.e. that the ketone functioning as nucleophile should attack the carbocation with its oxygen atom and not via its enol-*C*. Both the aurated aryl cation **IIa** and the aurated

vinyl cation **IIb** were attacked by the oxygen of the ketone used as solvent, which seemingly supports our hypothesis. In order to gain further insight into the control of selectivity of this transformation, a thermodynamic evaluation of the cyclization product and its potential isomers was conducted. For this, the conversion of 1,5-diyne **1h** into enol ether **3h** (Scheme 5) was used as basis for theoretical studies.



Scheme 5. Found attack of acetone via its carbonyl oxygen atom versus theoretical *C*-attack via its enol form.

Besides the hypothetical isomer **3h'**, its tautomers were also taken into consideration (Figure 6).

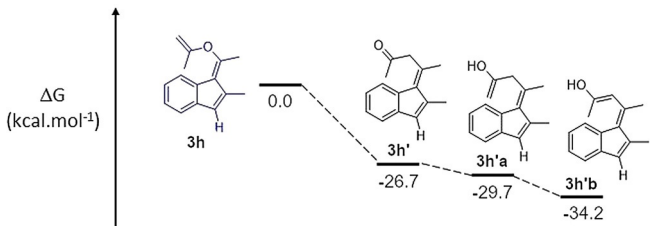


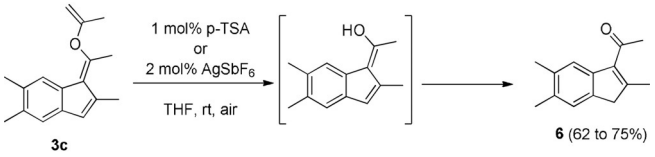
Figure 6. Thermodynamic evaluation of **3h** and its isomers (geometries were optimized using PBE/def2-SV(P) in the gas phase and energies were computed at the M06/def2-TZVPP level of theory).

This theoretical study shows, that **3h** is thermodynamically unfavored in relation to its potential isomers. That these isomers could not be detected hints at this transformation being under kinetic control. This stresses the preparative potential of aurated vinyl and aryl cations.

To the best of our knowledge, 6-(vinyloxy)fulvenes have not been synthesized before, yet they have much potential to become a substructure of interest, combining the chemistry of fulvenes[32] with the chemistry of vinyl ethers.[14] We evaluated some new transformations.

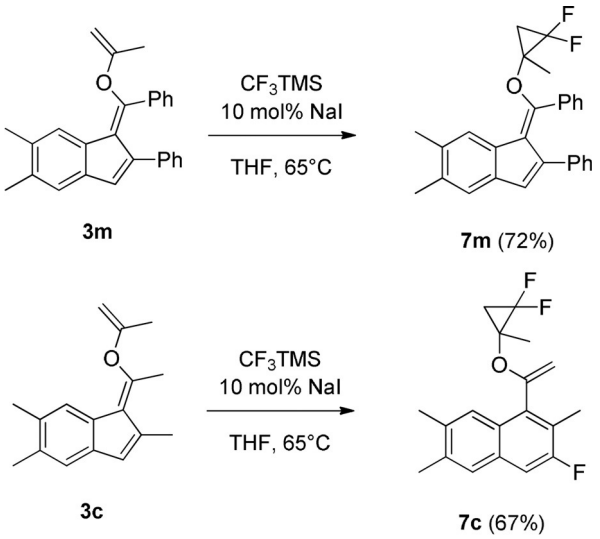
First, simple acidic hydrolysis of **3c** was tested. As expected, the vinyl ether functionality was lost. The released enol tautomerized to give the Michael system **6** in good yield (Scheme 6).

Since cyclopropanes[33] and fluorine[34] are of high interest in medicinal chemistry, we wanted to see if our new compound class could be subjected to the convenient difluorocyclopropanation established by Prakash et al.[35] To our delight we found



Scheme 6. Hydrolysis of vinyl ether **3c**.

that **3m** cleanly converts to the desired geminal difluorocyclopropane **7m** in good yield. For **3c**, on the other hand, the more complex product **7c** was isolated in good yield (Scheme 7).



Scheme 7. Reaction of 6-(vinyloxy)fulvenes with in situ-generated difluorcarbene.

Here too, the proposed structure for **7c** could be confirmed by X-ray crystallography (Figure 7).

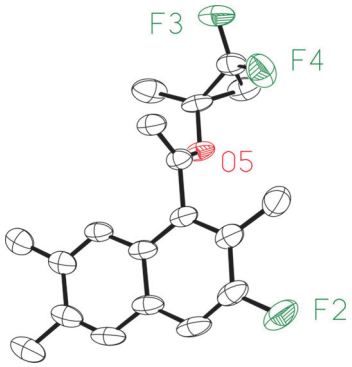
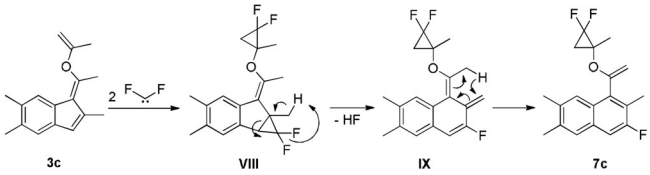


Figure 7. Solid state molecular structure of **7c**.[28] Hydrogen atoms were omitted for clarity.

The carbene intermediate does not only attack the vinyl moiety but also the double bond on the indene substructure, giving intermediate **VII**. This polycycle eliminates HF while undergoing a ring expansion. Similar halogenating ring expan-

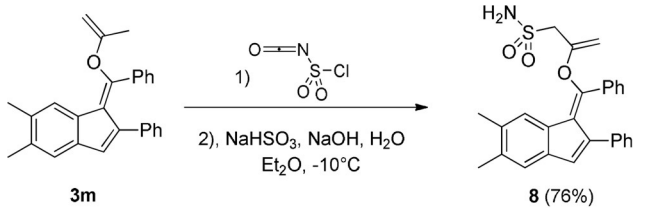
sions have been studied by Volchok et al.[36] The resulting intermediate **IX** rearranges to **7c** via an intramolecular Alder-ene reaction (Scheme 8).



Scheme 8. Proposed mechanism for the formation of **7c**.

Using only 0.7 equiv. of CF_3TMS gave a mixture of **3c**, monocyclopropanated product and **7c** as determined by GCMS. While this ring expansion of indene has been previously reported, this kind of reactivity on benzofulvenes has not been observed yet. Literature-known rearrangements of fulvenes to arenes follow harsh reaction conditions or require special substitution patterns.[37]

Another compound class of considerable interest is the broad family of sulfonamides, whose synthesis is a crucial point in medicinal chemistry, as they appear in numerous biologically active compounds. In fact, amide formation is one of the most important synthetic steps in the pharmaceutical industry.[38] To convert 6-(vinyloxy)fulvenes into this interesting functional group, **3m** can be left to react with CSI (Scheme 9).



Scheme 9. Synthesis of sulfonamide **8** starting from **3m**.

Sulfonamide **8** was obtained in good yield after an aqueous work up and recrystallization, making for a convenient synthesis of an interesting compound. In the observed transformation, the vinyl ether moiety acts as a *C*-nucleophile, attacking CSI under substitution of chloride. This reactivity has been observed using organostannanes as nucleophiles for example, in Friedel–Crafts type *ipso* substitutions.[39] The for olefins more common formation of β-lactams via a [2+2] cycloaddition[40] could not be observed, making for an unusual selectivity. Crystals suitable for X-ray single crystal structure analysis were gained by crystallization from DCM/ pentane at 4 °C, confirming the structure (Figure 8).[28]

Conclusions

Within the framework of our investigation, we established a mild novel synthesis of vinyl ethers from easy-to-make 1,5-diyne systems and ketones acting as reagent and solvent. This

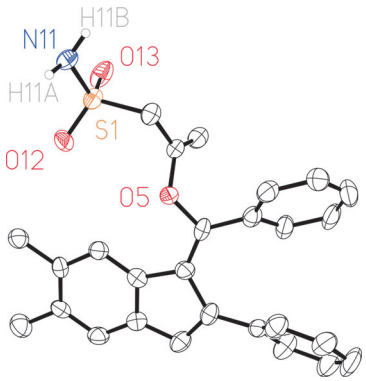


Figure 8. Molecular structure of **8** in the crystal.[28] Hydrogen atoms were omitted for clarity.

method utilizes aurated high energy species[12,13] and can be considered an otherwise difficult to access retrosynthetic disconnection. Hence, this gold-catalyzed transformation stands complementary to established methods.[27,16] The scope and limitations of this transformation have been studied by modifying the backbone and substituents on the alkynes. Overall thirteen novel vinyl ethers have been isolated in moderate to good yields, ranging between 32% and 78%. Within these studies, we discovered an unreported solvent controlled „switching" of the regioselectivity of a gold-catalyzed 6-*endo-dig* to a 5-*endo-dig* cyclization starting from 1,5-diynes. So far, such transformation modes have been strictly controlled by the substitution patterns of the starting material. Hints were gathered, that the polarity of the solvent is the key to this unusual selectivity, however hard evidence remains to be found.

Furthermore, the previously unknown substructure of 6-(vinyloxy)fulvenes is introduced and briefly evaluated regarding its chemistry. Mild and convenient functionalizations reveal a large potential for further transformations and applications in medicinal science. Fluorinated cyclopropanes and sulfonamides with an otherwise hard to access fulvene ether moiety can be prepared in good yield. The explored transformations show that in most cases a selective functionalization at the vinyloxy functionality and not the fulvene backbone is feasible. With this in mind these building blocks might also be of interest as monomers in polymer science.

The influence of solvent and potential applications for 6-(vinyloxy)fulvene are currently under investigation.

Experimental Section

General Procedure: Gold Catalytic Preparation of Vinyl Ethers: In a 4.5 mL vial taken from a drying oven, 1 equiv. of the diyne was dissolved in the respective, preferably dry, ketone (c_{diyne} = 150 μmol mL^{-1}) under air. 2.0 mol% IPr*Au(MeCN)SbF_6 was added and the vial sealed with a Teflon cap. The reaction mixture was stirred at rt until the reaction was finished, as confirmed by TLC. The reaction time usually ranged between 3 and 6 h. Overnight stirring lead to diminished yields or complete decomposition, depending on the compound. The solvent was removed in vacuo and the raw product was dissolved in DCM, Celite was added and the solvent removed again in vacuo. The raw product was purified

using column chromatography with silica gel, deactivated by NEt_3. In some cases, additional recrystallization from pentane was necessary.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aryl cations · fulvene ethers · gold catalysis · vinyl cations · vinyl ethers

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