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Carbene Transfer – A New Pathway for Propargylic Esters in Gold Catalysis

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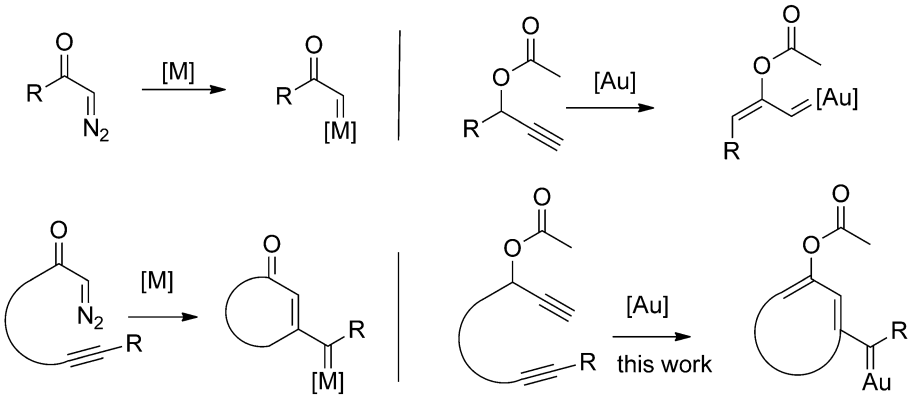
Abstract: Gold (homepage: http://www.hashmi.de) carbenes generated *via* 1,2-migration of a propargylic ester group can be transferred over a tethered alkyne. The use of aromatic backbones leads after a 1,7-carbene transfer to a benzyl-stabilized carbene as intermediate. A 1,2-shift of a methyl group delivers vinyl-substituted β-naphthol derivatives as the final products.

Keywords: carbene transfer; diynes; gold catalysis; 2-naphthols; propargylic esters

In the emerging field of gold-catalyzed reactions[1] one of the dominating aspects is the part which comprises the chemistry of gold carbenoids that can be generated *via* a 1,2-acetate shift of a propargylic ester moiety.

The so formed vinyl carbenes can be accessed under mild conditions which caught the attention of the chemical community as the propargylic esters can serve as substitutes for the hazardous and often explosive diazo compounds that are frequently used as precursors for the corresponding α-oxo carbenes (Scheme 1, upper part).[2] Based on this methodology, a whole series of beautiful transformations was reported recently and even various examples for applications in natural product synthesis can be found in the literature.[3] Interestingly, when we started our studies, no reports on the trapping of propargylic esters-derived carbenoids with a tethered alkyne were known. During the preparation of this manuscript one exciting contribution of the groups of Hirao and Chan appeared, which reports on the synthesis of 2,4a-dihydro-1*H*-fluorenes. This reaction cascade consists of a 1,2-migration of an acetoxy group followed by a carbene transfer over a pendent alkyne and finally a Nazarov-type cyclization as terminating step.[4] The first



Scheme 1. The generation of metal carbenoids and carbenoid transfer with alkynes.

example for a gold-catalyzed carbene transfer over an alkyne was described by the Toste group who used a diazo compound as carbene precursor.[5]

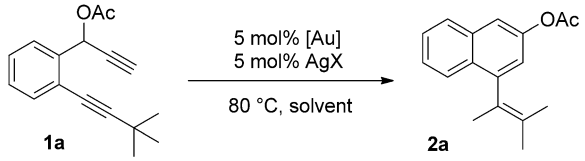
If one considers the plethora of useful synthetic transformations which are reported on metal-catalyzed carbene/alkyne transfer reactions based on the decomposition of diazo compounds,[6] we believe that there would be an immense impact if the more easily available carbene precursors could be applied for this type of chemistry (Scheme 1, lower part).

We envisioned that propargylic acetates might also be a perfect choice as starting materials since a 1,2-migration often can take place under remarkably mild conditions and furthermore the synthesis of the starting materials could be straightforward.

We decided to use aromatic backbones for our test substrates. The fixed geometry of the systems should enable clean reactions and, furthermore, the starting materials are accessible by a short route of simple transformations. A screening of the reaction conditions was performed with substrate **1a**, the results of the optimization are summarized in Table 1.

In a first set of experiments we applied air stable $IPrAuNTf_2$ in different solvents at a reaction temperature of 80 °C (entries 1–4). Indeed significant reactivity was observed for all of the applied solvents. Among the tested solvents DCE turned out to be the best choice (entry 4) but the GC yield of 44 % was still low. Next we investigated the effect of different counter ions (entries 5–8) but unfortunately no large counter ion effect was observed and yields were in the same moderate range. It is noteworthy that, by using the *in situ* activation with a silver salt, lower yields were obtained for the triflimide counter ion (entry 5). This can be rationalized by a competing decomposition of the starting material by the silver salt. Indeed the control experiment with only the silver salt showed a steady decomposition of the starting material. In order to circumvent this negative effect of the activation by silver, we switched back to isolated pre-activated triflimide complexes.[7] Changing the ligand to triphenylphosphane did not lead to an improvement (entry 10). Using the IPr-NHC ligand at room temperature delivered only 33% of the desired product (entry 11). Next we varied the concentration of the reaction mixture (entries 12 and 13). It became obvious that higher concentrations in combination with the IPr-NHC ligand led to a significant improvement of the yield. Finally, we screened non-activated gold sources for the transformation, too. To our surprise even IPrAuCl led to a quantitative conversion after 16 h at 80 °C (entry 14). In addition, yields turned out to be high. Encouraged by this rather uncommon reactivity we considered simple AuCl as catalyst (entry 15). By using this gold source, the reaction was speeded up remarkably and a full conversion was detected after only 0.2 h. In addition, an excellent yield of 97% was observed. It should be mentioned that in the case of Hirao and Chan's publication AuCl was *completely inefficient*, which indicates a strong catalyst dependency for these type of cyclizations.[4]

Table 1. Screening of the reaction conditions.



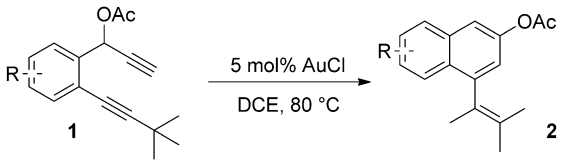
Entry	[Au]	AgX	Solvent	Time [h]	Yield[a] [%]
1	$IPrAuNTf_2$	–	benzene	0.5	27
2	$IPrAuNTf_2$	–	toluene	0.5	23
3	$IPrAuNTf_2$	–	MeCN	0.5	38
4	$IPrAuNTf_2$	–	DCE	0.5	44
5	IPrAuCl	$AgNTf_2$	DCE	0.5	34
6	IPrAuCl	$AgPF_6$	DCE	0.5	27
7	IPrAuCl	$AgSbF_6$	DCE	0.5	31
8	IPrAuCl	$AgBF_4$	DCE	0.5	35
9	–	$AgNTf_2$	DCE	0.5	decomposition
10	PPh_3AuNTf_2	–	DCE	0.5	41
11[b]	$IPrAuNTf_2$	–	DCE	1	33
12[c]	$IPrAuNTf_2$	–	DCE	0.5	57
13[d]	$IPrAuNTf_2$	–	DCE	0.5	65
14[d]	IPrAuCl	–	DCE	16	84
15[d]	AuCl	–	DCE	0.2	97

[a] Yield determined by GCMS using hexamethylbenzene as internal standard. ($c = 0.1$ mol/L).
[b] Reaction was run at room temperature.
[c] 0.25 mL solvent (0.19 mol/L).
[d] 0.125 mL solvent (0.38 mol/L).

2-D-NMR analysis of the obtained product **2a** revealed the formation of an acetate protected naphthol skeleton. As expected, the acetyl group performed a 1,2-shift leading to the oxygen in the β-position of the naphthol. Furthermore, the reaction must be terminated by a 1,2-shift of one of the methyl groups of the *tert*-butyl group, leading to a tetra-substituted vinyl substituent next to the ring fusion.

With the best reaction conditions in hand, we focused our attention on the evaluation of the reaction scope. At first, we briefly investigated the influence of different substitution patterns on the aromatic backbone (Table 2). Similar to the non-substituted backbone (**1a**) (entry 1) good to excellent yields were obtained for arene systems **1b–1e** bearing oxygen donor atoms (entries 2–5). An electron-donating methyl group in *para*-position to the substituent bearing the terminal alkyne was also well tolerated and the final product **2f** could be isolated in 85% yield (entry 6). Only slightly lower yields were obtained for electron-withdrawing substituents at the arene moiety, but yields were still high, no matter if fluoro (entries 7 and 8) or nitro groups (entry 9) were transformed. A

Table 2. Scope of the transformation.



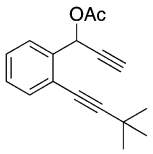
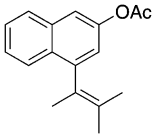
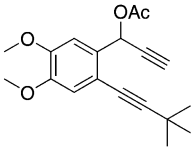
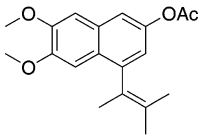
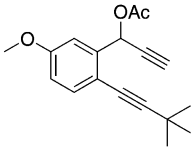
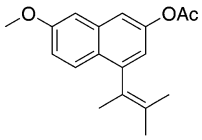
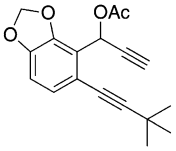
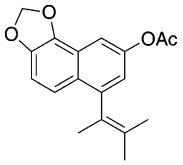
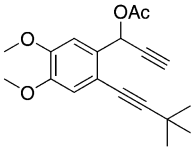
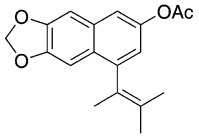
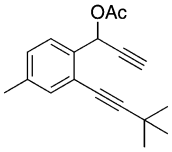
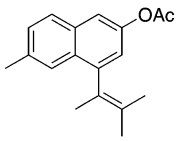
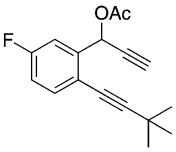
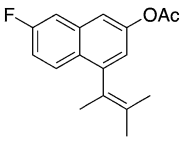
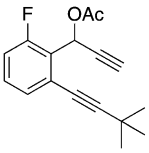
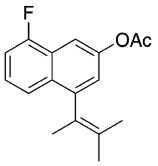
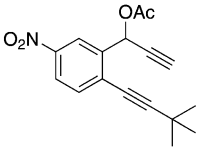
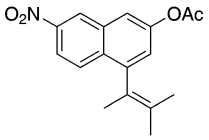
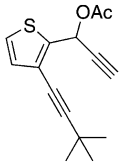
Entry	Substrate		Product		Time [min]	Yield [%]
1		**1a**		**2a**	15	94
2		**1b**		**2b**	20	85
3		**1c**		**2c**	120	99
4		**1d**		**2d**	30	88
5		**1e**		**2e**	180	80
6		**1f**		**2f**	120	85
7		**1g**		**2g**	120	72
8		**1h**		**2h**	120	71
9		**1i**		**2i**	120	81

Table 2. (Continued)

Entry	Substrate	Product	Time [min]	Yield [%]
10		**1j**	60	–[a]

[a] Starting material was recovered unchanged.

heteroaromatic thiophene backbone showed no conversion at all (entry 10). One reason might be the widened angle in the 5-membered ring which leads to a larger distance between the two reacting moieties.

Other migrating groups were also tested (Table 3). A migration of a pivaloyl moiety is also possible (entry 1), but the isolated yield for the product was slightly lower than for the corresponding acetyl derivative. No selective reaction was observed in the case of a trifluoroacetate group as migrating group (entry 2). This is not unexpected as to the best of our knowledge no successful gold-catalyzed 1,2-shifts have ever been reported for this moiety. Shifting to a benzoyl moiety restored the selectivity and a high yield of benzoyl-protected naphthol **2m** was obtained (entry 3). We were able to grow single crystals suitable for an X-ray crystal structure analysis. The solid state molecular structure which delivers the final proof for a correct assignment is depicted in Figure 1.[8]

Slightly lower yields were obtained with a *para*-nitrobenzoyl group which might be explained by the decreased nucleophilicity of the carbonyl oxygen (entry 4).

To expand the scope of the reaction substrate **3** was reacted under the optimized conditions (Scheme 2). Surprisingly, even though two competing pathways (hydride shift *vs.* methyl shift) are possible, only product **4** was observed. Under the same conditions that were applied previously only a low yield of 24% and no complete conversion were achieved. Even prolonged reaction times (20 h compared to 15 min for the corresponding *tert*-butyl substrate **1a**) did not deliver full conversion. The product was obtained as an inseparable mixture of **4** and the remaining starting material (**3**:**4** = 2:1).

Our mechanistic proposal, as exemplified for **1a**, is depicted in Scheme 3. The first step of the reaction cascade starts with the well known 1,2-migration of an acetyl group which is known to be favoured for terminal alkynes. The so formed vinyl carbene **III** can then undergo an intramolecular cyclopropenation event which might be assisted by the fixed geometry of intermediate **III**. The feasibility of this elementary step in gold-catalyzed reactions was previously described by the group of Davies, who reported on the intermolecular asymmetric cyclopropenation of internal alkynes with carbenoids derived from diazo compounds.[9] After gold-mediated ring opening of the cyclopropene unit,[10] benzyl cation **V** is formed. Breaking of the cyclopropane bond then generates the aromatic naphthyl skeleton and a stabilized carbenoid/cation intermediate **VI** is formed.[11] After a 1,2-migration of a methyl group, elimination of the gold catalyst closes the catalytic cycle under formation of the final product **2a**.

In conclusion, we have demonstrated that propargylic esters in the presence of a tethered alkyne can undergo a carbene transfer reaction which leads to a benzyl-stabilized carbenoid/cation if aromatic backbones are applied. The effective use of propargylic esters as carbenoid source for this type of chemistry should pave the way for further useful transformations. This process should be driven by the easier handling of the starting materials combined with a faster

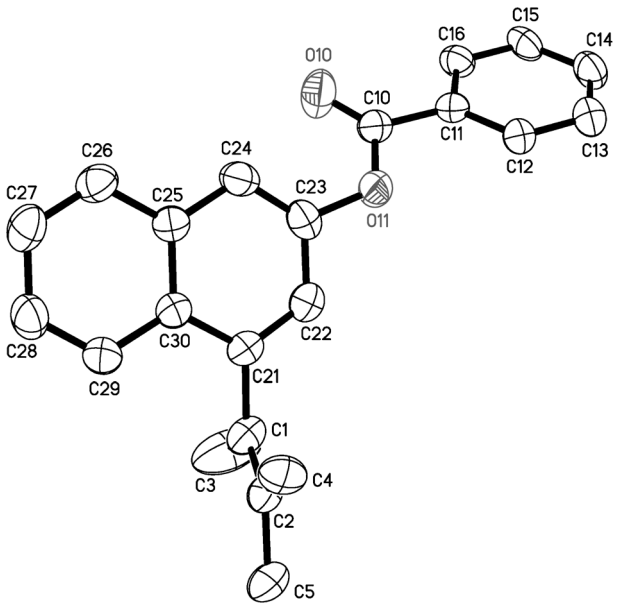
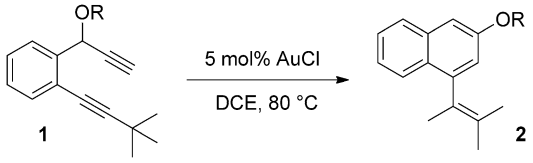
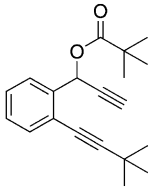
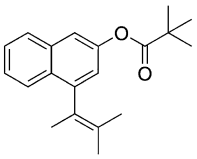
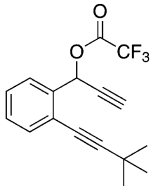
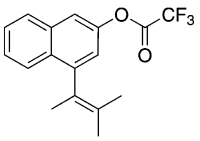
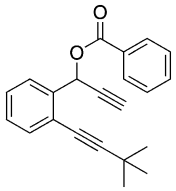
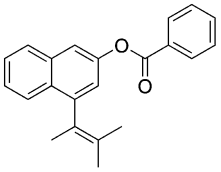
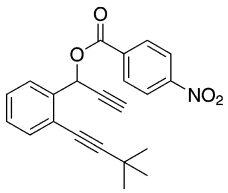
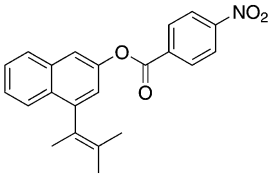


Figure 1. Solid state molecular structure of compound **2m**.

Table 3. Variation of the migrating group.



Entry	Substrate		Product		Time [min]	Yield [%]
1		**1k**		**2k**	240	85
2		**1l**		**2l**	60	–[a]
3		**1m**		**2m**	20	88
4[b]		**1n**		**2n**	180	42

[a] Unselective reaction.
[b] 10 mol% AuCl were employed.

access to potential starting materials. The search for other synthetically useful transformations based on this principle is ongoing in our laboratories.

Experimental Section

General Remarks

Chemicals were purchased from commercial suppliers and used as delivered. Dry solvents were dispensed from solvent purification system MB SPS-800. Oxygen-free, anhydrous reactions were carried out under an atmosphere of nitrogen. Reaction steps involving the synthesis of phosphorous ligands were carried out using dry and degassed solvents. To degas the solvents, nitrogen was bubbled through them for at least 1 hour.

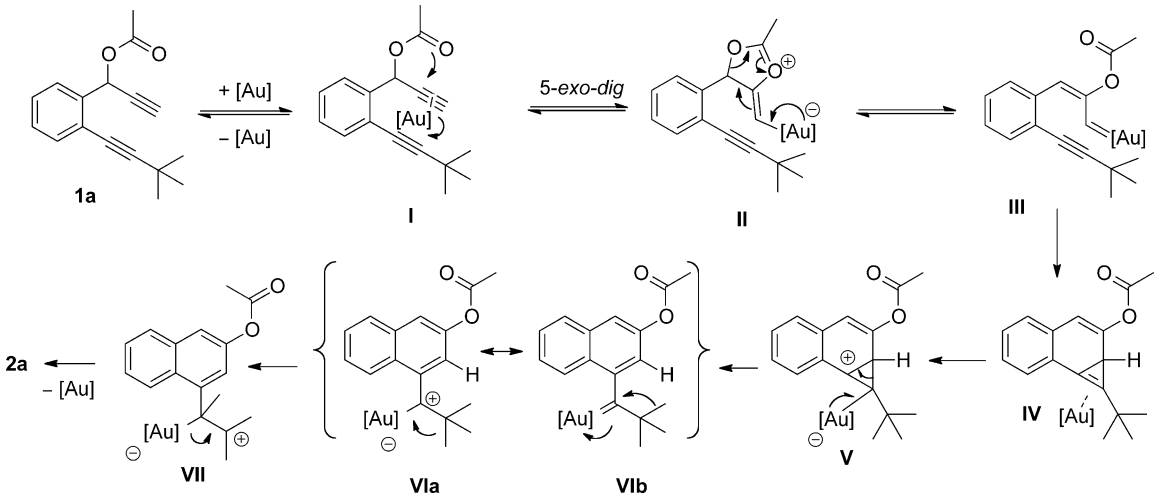
Scheme 2. Reaction of isopropyl substituted substrate **3**.

General Procedure 1 (GP1): Sonogashira Coupling

The aryl halide, 5 mol% of copper(I) iodide and 2.5 mol% of $PdCl_2(PPh_3)_2$ were dissolved in freshly degassed triethylamine under an atmosphere of nitrogen. After stirring for 10 min a small excess of the terminal alkyne was added. The resulting mixture was stirred at the mentioned temperature until the reaction was completed. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel.

General Procedure 2 (GP2): Grignard Reaction

Under an atmosphere of nitrogen the aldehyde was dissolved in THF. An excess of Grignard reagent was added



Scheme 3. Proposed mechanism.

and the mixture was stirred at room temperature until the reaction was completed. The reaction was quenched with aqueous saturated $NaHCO_3$ solution, extracted with DCM and dried over $MgSO_4$. The suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

General Procedure 3 (GP3): Introduction of an Acetyl Protecting Group

The diyne-ol, 1.10 equiv. DMAP and 1.10 equiv. NEt_3 were dissolved in DCM and 1.10 equiv. acetic anhydride were added under vigorous stirring. The reaction was monitored by TLC. After complete conversion of the starting material the reaction was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

General Procedure 4 (GP4): Gold Catalysis

400 μmol diyne were dissolved in 1 mL DCE. 20.0 μmol (5 mol%) AuCl were added under vigorous stirring and the mixtrure was heated to 80 °C. After complete consumption of the starting material the solvent was removed under reduced pressure and the crude product was purified by column chromatography.

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