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Gold Catalysis: β-Ketonaphthalenes *via* Molecular Gymnastics of 1,6-Diyne-4-en-3-ols

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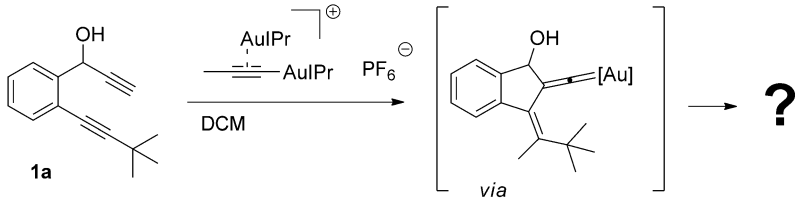
Abstract: 1,6-Diyne-4-en-3-ols with one terminal alkyne were applied as test substrates for a possible dual catalyzed cyclization. Instead of a dual catalysis cycle, naphthyl ketone derivatives were obtained as single products. The regioselectivity of the obtained products is unprecedented. Instead of the expected naphthyl ketones bearing the keto group in the α-position, the keto group is positioned in the ß-position of the naphthyl skeleton by a complex rearrangement of the starting materials.

Keywords: cycloisomerization; diynes; gold catalysis; rearrangement; regioselectivity

During the ongoing development of new synthetically useful transformations catalyzed by homogeneous gold catalysts,[1] substrates bearing two alkynyl moieties have attracted considerable interest in the recent past. Mainly two alternative reaction pathways can be found. The majority of the reactions is initiated *via* a nucleophilic addition onto one of the triple bonds. The double bond obtained then serves as a nucleophile and a subsequent reaction with the remaining alkyne delivers the final products. For this process *external*[2] as well as *intramolecularly*[3] offered nucleophiles were applied. Just recently Zhang's and our groups independently discovered a new reaction pathway for diyne systems, which is based on a dual activation mode. The nucleophilicity of one of the alkynes is increased *via* σ-coordination (acetylide formation). This enables the attack onto the remaining alkyne which is activated by a second cationic gold fragment *via* the common π-activation mode. Depending on the backbone of the diyne system either a 5-*endo*-dig cyclization or a 6-*endo*-dig cyclization takes place leading to highly reactive vinylidene/carbene intermediates with a rich follow-up chemisty.[4]

So far only 1,5-diynes were used as starting materials for these transformations. Now we have considered the easily available 1,6-diynes as starting materials as well. The unexpected results of these experiments are summarized in this contribution.

As test substrate we selected diyne **1a** as it is closely related to our previously published benzofulvene synthesis.[4d] As depicted in Scheme 1, we expected the formation of a gold vinylidene intermediate **I** which then could undergo a subsequent C–H insertion reaction. In order to initiate a dual activation mode, we employed a σ,π-dinuclear propyne gold acetylide (dual activation catalyst), a catalyst that had proven to be ideal for related reactions based on this reactivity.[5] Indeed we could monitor a complete conversion of the starting material even at room temper-



Scheme 1. Expected reactivity for substrate **1a**.

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ature, but to our surprise no C–H activation took place and the *tert*-butyl group was preserved in the final molecule (easily detectable by ^{1}H NMR). The NMR assignment revealed a naphthalene structure, but the substitution pattern of the product did not match with related systems derived from the cyclization of the corresponding non-terminal alkynes as starting materials; a reaction cascade that was reported by the Liu group.[6] Most fortunately, we were able to obtain single crystals suitable for an X-ray crystal structure analysis.[7] The solid state molecular structure in Figure 1 shows the unexpected outcome of this reaction. To our surprise the obtained naphthalene derivative **2a** contained the pivaloyl substituent in the β-position and furthermore a migration of the *tert*-butyl group must have taken place as the distance to both of the anellation points contains three carbon atoms!

In order to optimize the reaction conditions for this transformation, we first intended to evaluate whether a dual activation cycle or a classical π-activation mode is present. Therefore we synthesized preformed acetylide **3** and subjected it to catalytic amounts of cationic gold catalyst (Scheme 2). The fact that absolutely no conversion takes place indicates that a dual activation is unlikely. As a consequence we concentrated our efforts for catalyst optimization on cationic gold species without additives for acetylide formation (Table 1).

Results comparable to the dual activation catalyst (entry 1) were obtained with IPrAuCl in combination with the hexafluorophosphate counter ion (entry 2). Even better results were obtained with the triflimide counter ion. Under these conditions an excellent yield

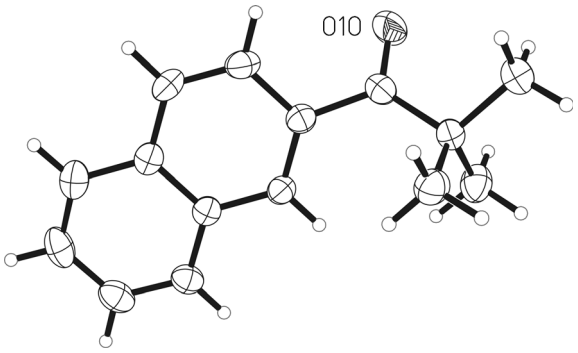
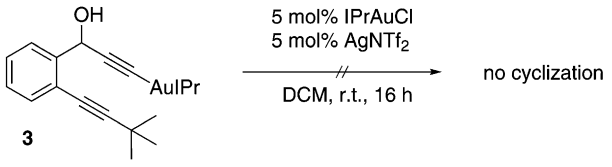
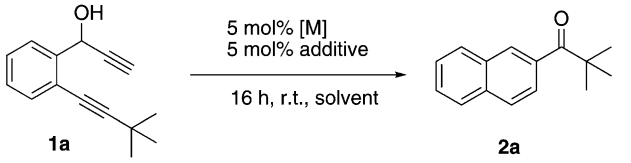


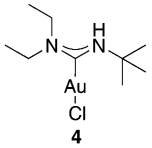
Figure 1. Solid state molecular structure of the product **2a**.



Scheme 2. Gold acetylide **3** does not react in the presence of active gold(I) catalyst.

Table 1. Screening of reaction conditions.



Entry	[M]	Additive	Solvent	Yield [%][a]
1	TDAC-PF_6	–	DCM	77
2	IPrAuCl	$AgPF_6$	DCM	77
3	**IPrAuCl**	**$AgNTf_2$**	**DCM**	**92**
4	IPrAuCl	$AgNTf_2$	acetone	traces
5	IPrAuCl	$AgNTf_2$	MeCN	traces
6	IPrAuCl	$AgNTf_2$	MeOH	89
7	IPrAuCl	$AgNTf_2$	benzene	61
8	IPrAuCl	$AgNTf_2$	toluene	67
9		$AgNTf_2$	DCM	13
10	BrettPhosAuCl	$AgNTf_2$	DCM	traces
11	SPhosAuCl	$AgNTf_2$	DCM	16
12	XPhosAuCl	$AgNTf_2$	DCM	traces
13	$(Mes)_3PAuCl$	$AgNTf_2$	DCM	32
15	$AgNTf_2$	–	DCM	traces
16	$FeCl_3$	–	DCM	–
17	$CuTf_2$	–	DCM	–
18	$DyTf_3$	–	DCM	–
19	$YbTf_3$	–	DCM	–
20	*p*-TsOH	–	DCM	–

[a] Yield determined by GC-MS using hexamethylbenzene as internal standard.

was obtained (entry 3). Changing the solvent did not improve the result. While only traces of product were obtained in acetone and acetonitrile (entries 4 and 5), methanol proved to be a suitable solvent, too (entry 6). Non-polar solvents like benzene and toluene delivered only moderate yields (entries 7 and 8). A short screening of different ligands at the gold center did not improve the yield. Neither the acyclic carbene complex **4** (entry 9) nor phosphane-based ligands (entries 10–13) showed acceptable results. Other Lewis acids (entries 15–19) or simple *para*-toluenesulfonic acid (entry 20) failed to catalyze the reaction.

With the optimized reaction conditions in hand we focused on the evaluation of the substrate scope (Table 2). Unfortunately, the isolated yield of the final product **2a** turned out to be only moderate which indicates problems during purification (entry 1). Substrates **1b** and **1c** bearing alkoxy groups in the *meta*-position to the alkynyl substitutens delivered only poor yields (entries 2 and 3), whereas regioisomer **1d** delivered acceptable results again. Electron-poor aromatic starting materials delivered better

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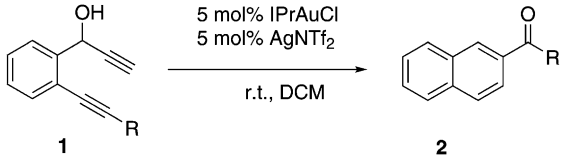
Table 2. Substrate scope.



1 **2**

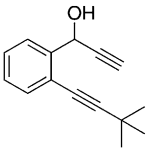
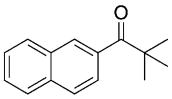
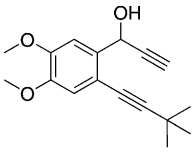
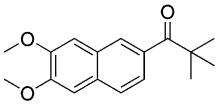
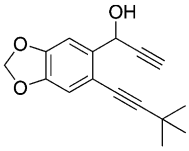
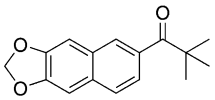
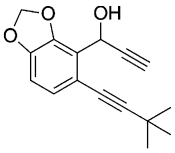
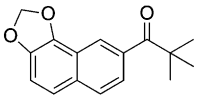
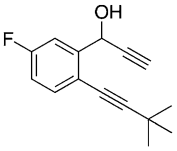
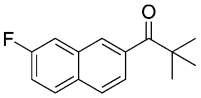
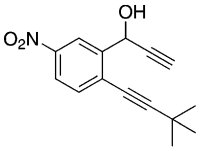
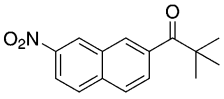
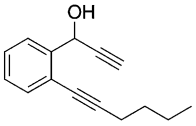
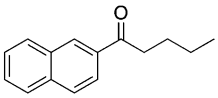
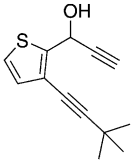
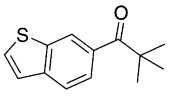
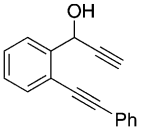
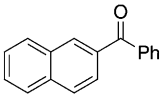
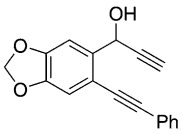
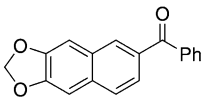
Entry	Substrate		Product		Time	Yield [%]
1		**1a**		**2a**	16 h	59
2		**1b**		**2b**	17 h	32
3		**1c**		**2c**	24 h	14
4		**1d**		**2d**	1 h	62
5		**1e**		**2e**	17 h	62
6		**1f**		**2f**	3 h	52
7		**1g**		**2g**	2 h	92
8		**1h**		**2h**	27 h	17
9		**1i**		**2i**	21 h	80
10		**1j**		**2j**	24 h	43

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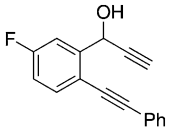
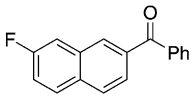
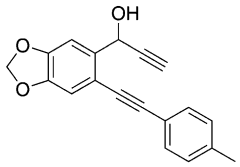
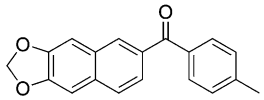
Table 2. (Continued)

Entry	Substrate		Product		Time	Yield [%]
11		**1k**		**2k**	24 h	65
12		**1l**		**2l**	16 h	51

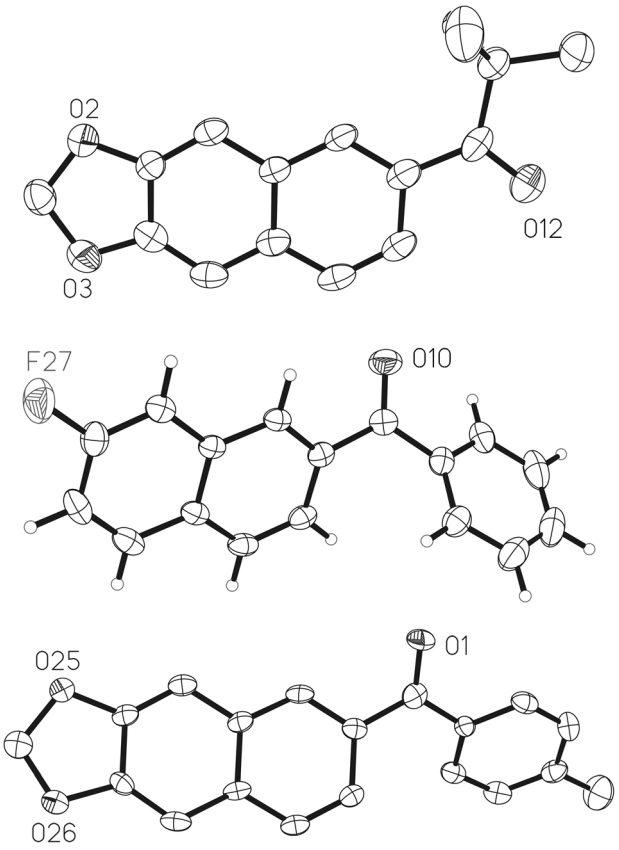
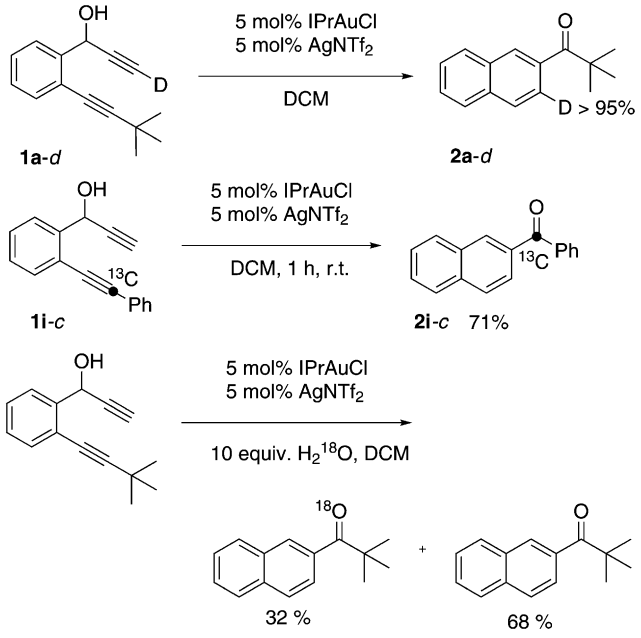


Figure 2. Solid state molecular structures of compounds **2c** (*top*), **2k** (*middle*) and **2l** (*bottom*).

yields and both fluoro and nitro substitutents were tolerated (entries 5 and 6). The use of a sterically less demanding unbranched alkyl chain as alkyne substituent was tolerated as well and product **2g** was obtained in excellent isolated yields (entry 7). Changing the aromatic backbone to thiophene delivered significantly lower yields than the corresponding benzene derivative (entry 8). Next we shifted to aromatic substituents at the alkyne terminus (entries 9–11). For all of the test substrates yields were higher for this substitution pattern no matter if there are electronically neutral (entry 9), electron-donating (entry 10) or electron-withdrawing substitutents (entry 11) at the aromatic backbone. Substituents at the arene at the alkyne terminus are also tolerated which was demonstrated by substrate **2l** (entry 12). In order to verify the correct assignment of the obtained structures, additional X-ray crystal structure analyses were performed. Figure 2 shows the solid state molecular structures of compounds **2c**, **2k** and **2l**.[7] The structure of **2l** demonstrates that the same substitution pattern is also obtained for aryl substitution at the internal alkyne. Structure **2k** demonstrates that the carbonyl is placed next to the former terminal alkyne position.

In order to obtain further insight into the reaction mechanism, deuterated substrate **1a**-*d* was converted under the standard reaction conditions (Scheme 3,



Scheme 3. Labelling experiments.

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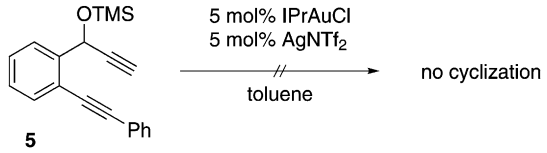
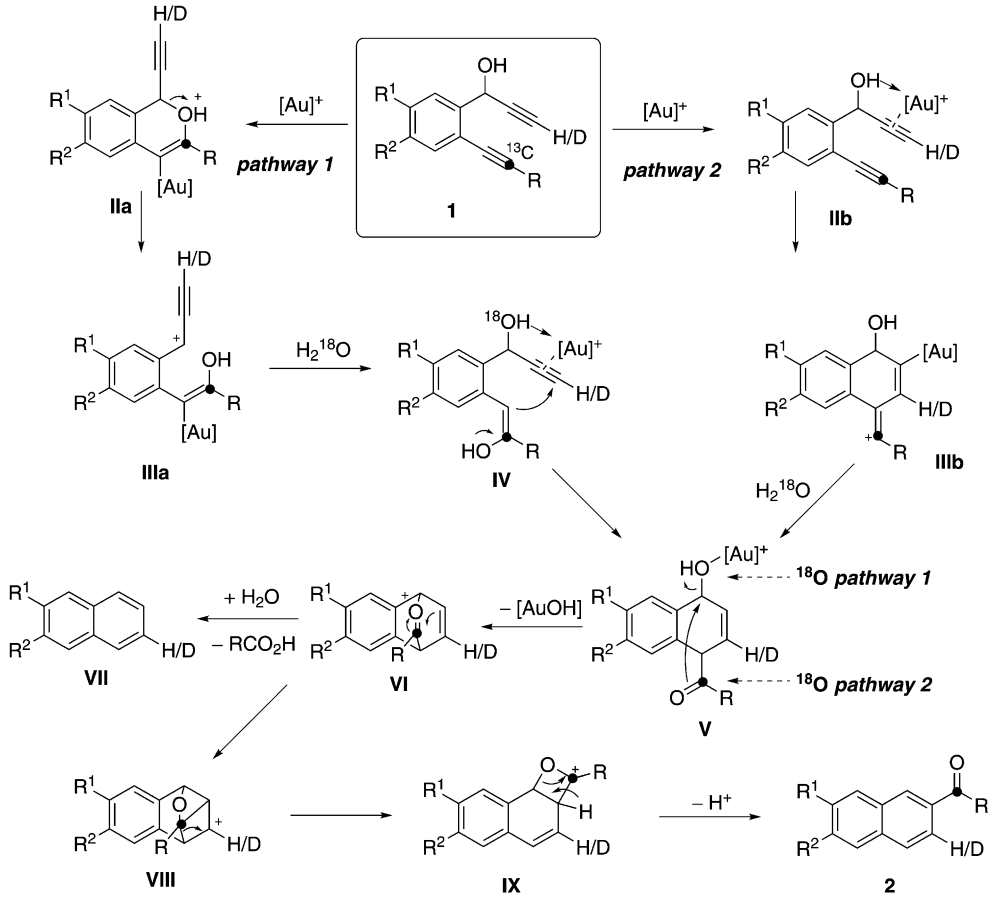
upper part). The deuterium labelling was completely preserved in the product with the deuterium labelling in the β-position of the naphthalene system next to the carbonyl carbon atom. In addition we converted substrate **1i**-*c* with ^{13}C-labelling at the alkyne terminus. As depicted in Scheme 3 (*middle part*) the labelled carbon is transferred to the carbonyl position of the final product **2i**-*c* (the position of the ^{13}C-labelled carbon was confirmed by an intense peak at 198.1 ppm in the carbon NMR; in addition the labelling was confirmed by mass spectrometry by the increased intensity of the molecule peak at $m/z = 233$ and its characteristic fragmentations at $m/z = 156$ $[C_{10}{}^{13}CH_7O]^+$ and 106 $[C_6{}^{13}CH_5O]^+$; fragmentation ions without the CO of the carbonyl group match with the natural ^{13}C distribution. To evaluate the origin of the oxygen in the product, we conducted the reaction under dry conditions in the presence of 10 equivalents of $H_2{}^{18}O$ (Scheme 3, *lower part*). Even in the presence of the great excess of oxgen labelled water, only minor amounts were incorporated in the final product. This strongly indicates that the oxygen is transferred in an intramolecular process.

Finally, we examined the reaction with trimethylsilyl-protected alkynol **5** (Scheme 4). For this type of substrate no cyclization took place which underlies the importance of the hydroxy moiety for the rearrangement.



Scheme 4. No reaction with TMS-protected substrate **5**.

Our mechanistic proposal is depicted in Scheme 5. For the first part of the transformation two different pathways are reasonable.[8] Pathway 1 is initiated by a nucleophilic attack of the propargylic hydroxy group onto the non-terminal alkyne leading to intermediate **IIa**. The next step involves a cleavage of the ether bond under formation of stabilized cation **IIIa**.[9] The benzylic cation can then be trapped by a molecule of water which stems from the reaction solvent. This overall process of a S_N1-type propargylic substitution is a well known process in gold chemistry.[10] The so formed intermediate **IV** contains a nucleophilic enolate moiety which can attack the π-actitvated terminal alkyne under formation of key intermediate **V**. The



Scheme 5. Mechanistic proposal.

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same key intermediate **V** could also be formed *via* pathway 2. The initial reaction steps for this pathway are akin to those proposed by the Liu group.[6,11] The hydroxy moiety in the starting material might direct the cationic gold fragment to the internal position of the terminal alkyne which then enables a 6-*endo*-dig attack of the non-terminal alkyne. The so formed cationic vinyl gold species **IIIb**[9] reacts with traces of water in the solvent which after tautermerization also delivers ketone **V** as key intermediate. It should be mentioned that in the case of labelled water in the reaction media two different positions in intermediate **V** are labelled. Pathway 1 should put the labelled oxygen in the benzylic position while a nucleophilic attack of water onto cation **IIIb** would place the labelled oxgen at the carbonyl position. The next step of the cascade comprises the nucleophilic attack of the carbonyl oxygen onto the benzylic position. It is reasonable that gold is also involved in this step and that the cationic gold fragment triggers the release of the hydroxy group under formation of a gold hydroxy complex. The so formed oxonium intermediate **VI** is then attacked by the adjacent double bond. Unsubstituted naphthalene by-products **VII** could also be observed in small amounts. These by-products were also observed by the Liu group and can be explained by water induced decomposition of intermediate **VI** under elimination of a molecule of organic acid. It remains unclear why this reaction step only occurs in traces and cannot be forced to be the major pathway for our substrates (even in the presence of 10 equivalents of water). Instead of the elimination pathway mainly charged intermediate **VIII** is formed which then undergoes rearrangement to the aromatic products under release of a proton. If one consideres the labelling experiments both of the pathways are in line with the carbon and deuterium labelling, but the results of the oxygen labelling which underline that an intramolecular oxygen transfer takes place strongly favour pathway 1.

In conclusion, we could present a new mechanistic pathway in the field of diyne cyclizations. By the use of a terminal alkyne, naphthyl ketone derivatives with a completely different substitution pattern than the products of related transformations can be obtained by an unusual migration of the alkyne substituent. It remains a challenge to explore the concrete reason for this change in reactivity. Further studies addressing this question are ongoing in our laboratories.

Experimental Section

General Procedure for the 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 1.2 equivalents of the terminal alkyne were 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 for the Grignard Reaction

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

The diynol was dissolved in a small amount of DCM. 5 mol% IPrAuCl and 5 mol% $AgNTf_2$ were added under vigorous stirring and the reaction was monitored by TLC. 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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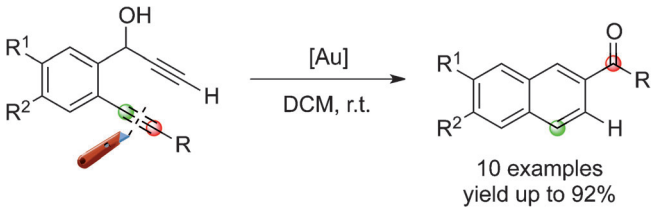

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