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Gold Catalysis: Tandem Reactions of Diyne–Diols and External Nucleophiles as an Easy Access to Tricyclic Cage-Like Structures**

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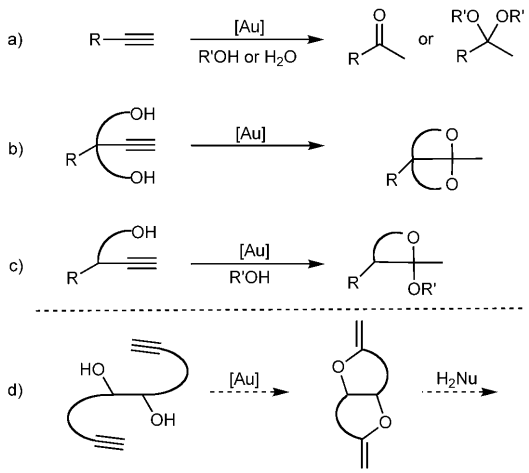
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: Different diyne–diols composed of two terminal homopropargylic alcohol groups were prepared by bi-directional synthesis. Subjection of the *syn* diastereomers to NAC–gold catalysts (NAC = nitrogen acyclic carbene) in the presence of external nucleophiles such as water or anilines provided substituted and highly rigid heterocyclic cages. The corresponding *anti* disastereomers polymerised. An intermediate of the reactions of the *syn* diastereomers could be isolated and even be characterised by crystal structure analysis. Overall, eight new bonds are formed in the reaction, which proceeds by a multistep sequence of highly selective hydroalkoxylations and hydrohydroxylation or hydroaminations. For furyl substituents and for internal alkynes competing reaction pathways could be identified. By the cross-coupling of a product with an iodoaryl substituent, the use of these cage compounds as geometrically defined linking groups by using orthogonal transition-metal-catalysed methodology, namely, gold and palladium catalysis, could be demonstrated.

Keywords: alcohols · alkynes · amines · gold · heterocycles

Introduction

In recent years numerous new gold-catalysed reactions have been reported, and this interesting area of organic chemistry is still one of the hot topics in current chemistry.[1] The initial step in most of the gold-catalysed reactions is the activation of an alkyne by the carbophilic metal centre, followed by the attack of a nucleophile. The first reports on this reactivity pattern were published nearly 20 years ago by Utimoto et al.[2] Besides the addition of nitrogen nucleophiles, they could show that water and alcohols could serve as nucleophiles as well, thus leading to ketones and acetals as products (Scheme 1a). In the last decades the intermolecular hydroalkoxylation and the hydration of alkynes became one of the benchmark reactions in gold catalysis.[3] In addition to the intermolecular reactions, a wide range of intramolecular cyclisations were established, leading to structurally complex acetals, ketals and spiroketals (Scheme 1b).[4] Furthermore,



Scheme 1. Hydroalkoxylation and hydration pathways of alkynes.

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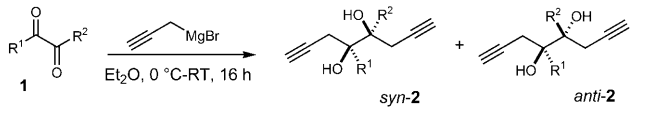
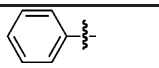
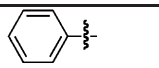
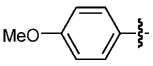
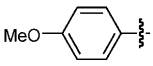
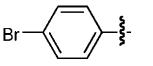
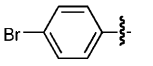
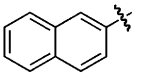
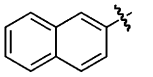
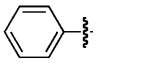
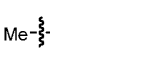
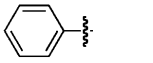
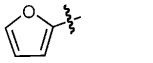
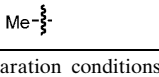
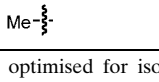
combinations of an intramolecular enol ether formation followed by a subsequent intermolecular trapping with various alcohols were described (Scheme 1c).[4b,g,5] A very elegant and visionary variation of this principle has been reported by Barluenga et al.[6] Considering the above-mentioned reaction pathways, we were curious to know if it was possible to use diyne–diols with a suitable distance between the reacting groups to induce a selective mono attack of the hydroxyl groups (Scheme 1d). A formation of bicyclic bis(enol ethers) should lead to reactive intermediates that could allow an entry for further transformations.

Results and Discussion

As a source for possible bis(enol ether) intermediates, the diols **2** were prepared by a twofold addition of propargyl Grignard reagent to the readily available 1,2-diketones **1** (Table 1). Products **2** were obtained as a mixture of diastereomers, which in most cases were formed in a ratio close to 1:1, the only exception being the methyl-substituted diol **2g** (80%, *anti*; Table 1, entry 7). Because parts of the *anti* isomer could easily be separated by crystallisation (except for methyl-substituted diol **2g**, Table 1, entry 7), the isolated yields are given for the enriched *syn* isomers. The structural assignment of the *syn* isomers is based on the comparison of the NMR data and the configuration observed in several X-ray crystal structure analyses.[7,8] As one representative example, Figure 1 displays the solid-state structure of *syn*-**2b** (other solid-state structures of *syn*-diols **2c** and **2f** have been obtained, too).[7] The propargyl side chain shows two different orientations in the solid state.

Table 1. Bidirectional synthesis of diols **2**.



Entry	R^1	R^2	Crude d.r. (*syn*:*anti*)	**2**	Yield **2** [%][a]	Isolated d.r. (*syn*:*anti*)
1			44:56	**a**	50	84:16
2			50:50	**b**[c]	25	75:25
3			44:56	**c**[c]	42	91:9
4			60:40	**d**	42	92:8
5			–[b]	**e**	49	92:8
6			50:50	**f**[c]	25	92:8
7			20:80	**g**	80	40:60

[a] Separation conditions optimised for isolation of *syn*-**2**. Parts of the *anti* isomers were removed by crystallisation during the isolation process. [b] Complex mixture. [c] X-ray structure determination.[7]

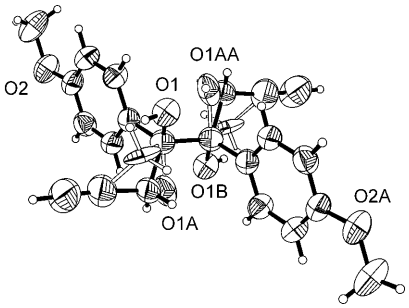
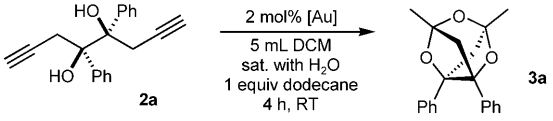
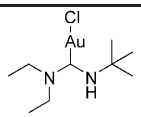
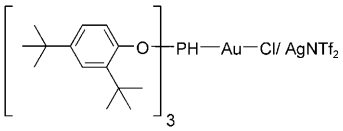


Figure 1. Solid-state molecular structure of **2b**.

With the *syn*-diols in hand, we first tested the conversion of **2a** with several gold(I) catalysts as well as simple gold(III) chloride. All the reactions were performed in dichloromethane saturated with water. One equivalent dodecane was used as an internal standard and the results are summarised in Table 2. Besides the acetate-coordinated triphenylphosphine gold(I) complex (Table 2, entry 6), all of the tested gold compounds (for example, the in situ activated phosphite-based catalyst (Table 2, entry 2) or the preformed $Ph_3PAuNTf_2$ (Table 2, entry 3)) showed significant reactivity. The best results were obtained by using the activated NAC–complex (Cat A, Table 2, entry 1; NAC = nitrogen acyclic carbene).[9] The conversion with $AuCl_3$ was significantly less efficient, and for $AgNTf_2$ only traces of product were obtained even after prolonged reaction times.[10]

Table 2. Catalyst screening.



Entry	Catalyst	Standard:Product
1	 Cat A / $AgNTf_2$	1:1
2		1:0.65
3	$Ph_3PAuNTf_2$	1:0.70
4	$AuCl_3$	1:0.26
5	nBuAd$_2$PAuNTf$_2$	1:0.71
6	$Ph_3PAuOAc/AgNTf_2$	1:0
7	IPrAuCl/$AgNTf_2$	1:0.82
8	$AgNTf_2$	1:0
9	H-KITPHOSAuNTf$_2$[11]	1:0.76
10	Cy$_2$BiphenylAuNTf$_2$[11]	1:0.82

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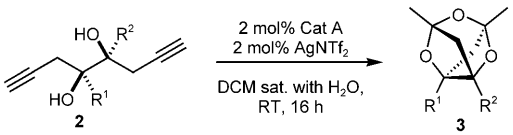
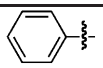
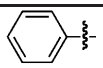
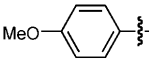
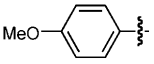
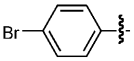
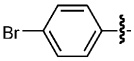
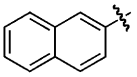
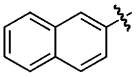
Conversion of the test substrate **2a** on a preparative scale under the optimised conditions allowed the identification of the reaction product. The product **3a** was obtained exclusively in high yield (Table 3, entry 1). Fortunately, the product delivered crystals that were suitable for an X-ray crystal structure analysis.[7] Figure 2 displays the solid-state structure of **3a**, which unambiguously proves the formation of a new type of cage-shaped tricyclic ketal. Unfortunately, the conversion of *anti*-**2a** only resulted in decomposition, most probably due to polymerisation of the intermediate enol ethers.

Table 3. Substrate scope for the tandem ketalisation.



Entry	R^1	R^2	3	Yield of 3 [%]
1			**a**[a]	82
2			**b**[a]	75
3			**c**[a]	79
4			**d**[a]	69
5			**e**	58
6			**f**	48

[a] X-ray structure determination.[7]

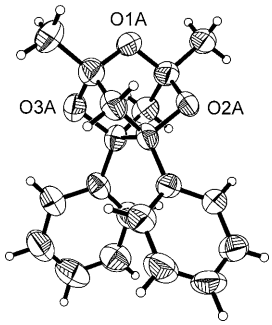
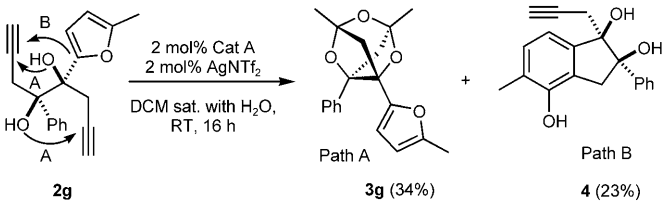


Figure 2. Solid-state molecular structure of **3a**.

To get an impression of the substrate scope, a range of *syn*-diols **2** were converted in preparative scales. Both an electron-donating (Table 3, entry 2) and a bromo substituent (Table 3, entry 3) at the aromatic system were tolerated. Switching to the bulkier naphthyl substituent (Table 3, entry 4) still delivered good yields. Next we investigated alkyl-substituted diol **2e** (Table 3, entry 5), which was also readily converted, but gave slightly lower yields. The combination of aryl and alkyl substituents in substrate **2f** also delivered the desired product in moderate yield (Table 3, entry 6). All products are crystalline solids, in addition to **3a** the three products **3b**, **3c** and **3d** could be characterised by crystal structure analyses.

Finally, substrate **2g** that contains a furan–yne substructure was converted (Scheme 2). In this case two competing reaction pathways are possible. In addition to the product **3g** of the domino ketalisation process (initiated by the oxygen attack, Path A), a competing furan–yne cyclisation (attack of the furan double bond, Path B) was observed, leading to significant amounts of phenol **4**.[12] Owing to the *syn* arrangement of the hydroxyl groups of phenol **4**, no further cyclisation is possible. Owing to the mild reaction conditions, a gold-catalysed intermolecular addition of water to the alkyne was also not observed. The structure of **4** is also based on a crystal structure analysis (Figure 3).



Scheme 2. Competing reaction pathways for substrate **2g**.

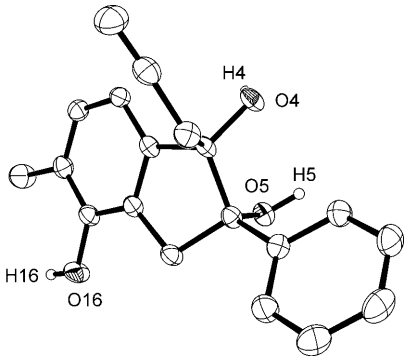


Figure 3. Solid-state molecular structure of **4**.

Encouraged by the results for the ketalisation process, we considered the possibility of using other external nucleophiles than water for incorporation as the bridging atom. For an initial catalyst screening, we tested the reaction with substrate **2a** and three equivalents of aniline as the nucleophile under different reaction conditions. The results are presented in Table 4. NHC ligands as well as NAC ligands showed good conversions with the NTf_2 counterion, with only a minor influence of the solvent. The reaction times for the aniline additions were longer: after 3 h still no complete conversion was observed for all of the tested catalyst systems. The optimum conditions were found to be the NAC–

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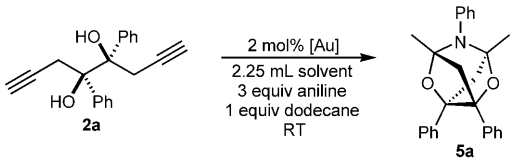
Table 4. Catalyst optimisation for intermolecular nitrogen nucleophiles.



Entry	Catalyst	AgX	Solvent	Standard:Product after 3 h	Standard:Product after 72 h
1	IPrAuCl	$AgNTf_2$	DCM	1:0.53	1:0.75
2	Cat A	$AgNTf_2$	DCM	1:0.57	1:0.69
3	IPrAuCl	$AgNTf_2$	toluene	1:0.53	1:0.70
4	Cat A	$AgNTf_2$	toluene	1:0.59	1:0.78
5	IPrAuCl	$AgNTf_2$	acetonitrile	1:0.53	1:0.88
6	Cat A	$AgNTf_2$	acetonitrile	1:0.43	1:1
7	IPrAuCl	$AgSbF_6$	DCM	1:0	1:0
8	Cat A	$AgSbF_6$	DCM	1:0	1:0
9	IPrAuCl	$AgSbF_6$	toluene	1:0	1:0
10	Cat A	$AgSbF_6$	toluene	1:0	1:0

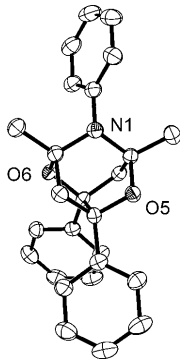
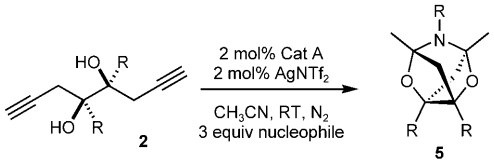


Figure 4. Solid-state molecular structure of **5a**.

catalyst (Cat A) activated with $AgNTf_2$ in acetonitrile (Table 4, entry 6). A massive counterion effect was visible by changing the counterion to hexafluoroantimonate; in these cases no reaction took place under various conditions (Table 4, entries 7–10).

Under the optimised conditions different N nucleophiles were subjected to the diols **2**. Table 5 gives an impression of the synthetic potential and the limitations. Starting with simple aniline (Table 5, entry 1), we were pleased to obtain promising results for N nucleophiles as well. As in the case of the water addition, a high yield of 80% was achieved. Once again the results of the X-ray crystal structure analysis delivered the proof for the structural assignment of the resulting tricyclic system (Figure 4 for **5a**).[7] Changing the substituents at the starting diols to alkyl dramatically reduced the reactivity. No complete conversion was observed for the addition of aniline, even after prolonged reaction times, and therefore only 15% of the desired product **5b** could be isolated (Table 5, entry 2). As a result, we switched back to aromatic diols again. First we tested alkyl-substituted anilines. In the cases of a mono substitution, high yields were obtained for *ortho*-, *meta*- and *para*-substituted anilines (Table 5, entries 3–7). In the case of *o*,*o*-

Table 5. Reaction of different substrates **2** with different nitrogen nucleophiles.



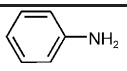
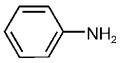
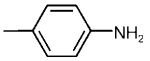
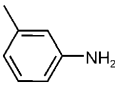
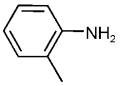
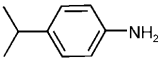
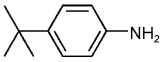
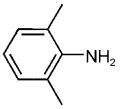
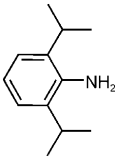
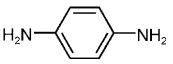
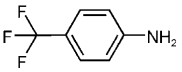
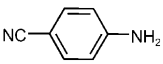
Entry	2	Nucleophile	Product	Yield [%]	Time
1	**a**		**5a**[b]	80	16 h
2	**e**		**5b**[b]	15[c]	16 h
3	**a**		**5c**[b]	96	3 d
4	**a**		**5d**	82	2 d
5	**a**		**5e**	81	5 d
6	**a**		**5f**[b]	80	16 h
7	**a**		**5g**[b]	85	16 h
8	**a**		**5h**	18	2 d
9	**a**		–	unselective	2 d
10	**a**		–	no reaction	6 d
11	**a**		**5i**[b]	76	16 h
12	**a**		**5j**	77	16 h

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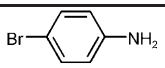
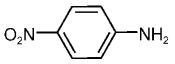
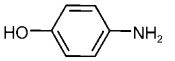
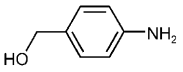
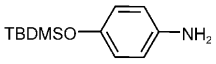
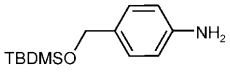
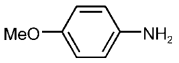
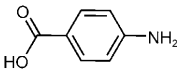
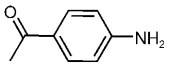
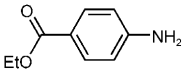
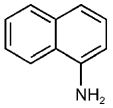
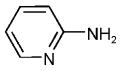
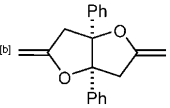
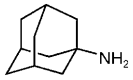
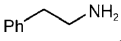
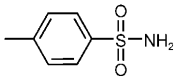
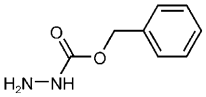
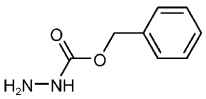
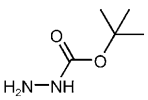
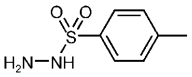
Table 5. (Continued)

Entry	2	Nucleophile	Product	Yield [%]	Time
13	a		**5k**	85	16 h
14	a		–	slow decomposition	11 d
15	a		–	no reaction	5 d
16	a		–	no reaction	2 d
17	a		**5l**[b]	59	28 d
18	a		**5m**	52	2 d[a]
19	a		**5n**	84	16 h
20	a		**5o**	45	16 h
21	a		**5p**[b]	81	16 h
22	a		–	no reaction	4 d
23	a		**5q**	88	16 h
24	a		**5r**[b] and	33	14 d
			6[b] 	39	
25	a		–	no reaction	4 d
26	a		**6**	25[c]	7 d[a]
27	a		–	unselective	1 d
28	a		**5s**	99	16 h
29	c		**5t**	71	2 d
30	a		**5u**	63	16 h
31	a		**5v**	52	16 h

[a] 60 °C. [b] X-ray structure determination.[7] [c] Incomplete conversion.

disubstituted anilines, a significant drop in yield was observed for the dimethyl case (Table 5, entry 8) and the reaction with sterically more demanding isopropyl groups only revealed unselective reactivity (Table 5, entry 9). Next we explored the functional-group tolerance. Although a second amino functionality was not tolerated (Table 5, entry 10), no problems occurred with electron-deficient trifluoromethyl-, nitrile- and bromo-substituted anilines, all of them delivering high yields (Table 5, entries 11–13). In that series, a nitro substituent was the limit (Table 5, entry 14). Probably due to the strong electron-withdrawing effect, only minor conversion and poor selectivity was observed. Substrates with additional unprotected hydroxy functions were also not suitable (Table 5, entries 15 and 16). Surprisingly, no reaction took place even after several days. Most probably this is caused by a reduction of the catalyst by the substrate; the silyl-protected derivatives (Table 5, entries 17 and 18), as well as a methyl ether derivative (Table 5, entry 19), could, however, be converted in reasonable yields. Although an unprotected acid moiety as well as a ketone were tolerated at the *para* position of the aromatic ring (Table 5, entries 20 and 21), *p*-aminobenzoic acid ethyl ester (Table 5, entry 22) showed no reactivity. Changing the aromatic system of the nucleophile was also possible; α-naphthylamine smoothly delivered the desired product (Table 5, entry 23), and even electron-deficient 2-aminopyridine showed moderate conversion after prolonged reaction times (Table 5, entry 24). In the case of 2-aminopyridine, we were able to isolate significant amounts of bicyclic double enol ether **6**. The solid-state structure of this intermediate (see below) nicely shows the open-cage structure of these systems. Although adamantyl amine showed no reactivity (Table 5, entry 25), intermediate **6** could be isolated with phenethylamine as the nucleophile (Table 5, entry 26)

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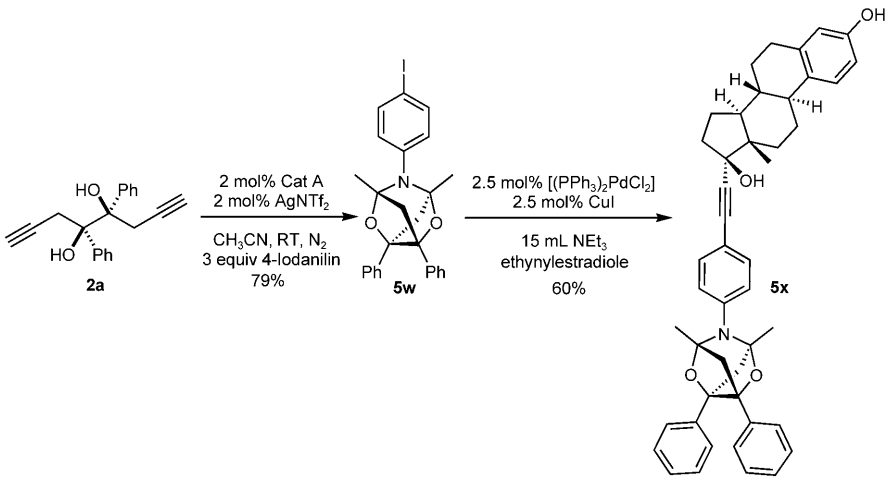
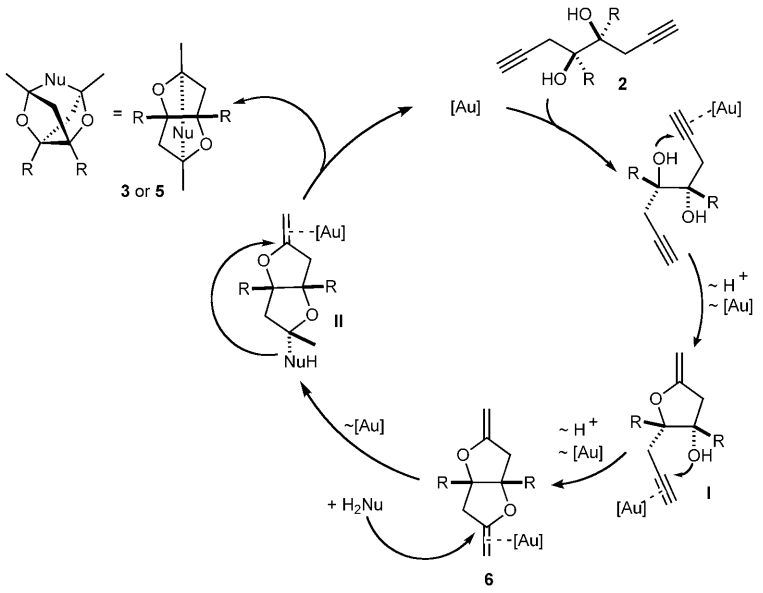
but incomplete conversion, even under elevated temperatures, limited the yield. Still, this is a unique case because **6** represents one of the few cases in which intermediates of gold-catalysed conversions can be isolated and fully characterised.[13] The conversion of tosylamide failed probably owing to its decreased nucleophilicity (Table 5, entry 27). Finally, we tested hydrazine derivatives as nucleophiles. Good to excellent results were obtained for benzylcarbazate (Table 5, entries 28 and 29), and *tert*-butyl carbazate as well as tosylhydrazine also delivered satisfying results (Table 5, entries 30 and 31). This opens the possibility for further functionalisation at these positions.

By the incorporation of *p*-iodoaniline in the resulting tricycle **5w**, a substrate that can easily be modified through cross-coupling methods, was obtained (Scheme 3). To demonstrate the access to complex molecular structures by using the orthogonality of two metals, **5w** was converted under Sonogashira conditions. Coupling with ethynylestradiole accomplished the modified tricycle **5x** in 60% yield.

Overall, many of the substrates could be characterised by single-crystal structure analyses, namely, **5b**, **5c**, **5f**, **5g**, **5i**, **5l**, **5p** and **5r**.



Scheme 3. Further modifications of tricycles **5** through cross-coupling.



Scheme 4. Mechanistic hypothesis for the tandem cyclisation.

Our mechanistic hypothesis is illustrated in Scheme 4. As mentioned in the introduction, the first intramolecular hydroalkoxylation by the tethered hydroxyl function is initiated by the π coordination of the gold catalyst. The tether length of the second hydroxyl moiety in the resulting enol ether **I** now circumvents the usual reaction pathway (Scheme 1b). Instead of the more reactive, activated[14] enol ether part (which would lead to acetal formation), the tether length means that the molecule is predestined for a second intramolecular nucleophilic attack to the alkyne, the second hydroalkoxylation, to form intermediate **6**. As mentioned above, we indeed succeeded in isolating **6** and even characterising this crucial intermediate[13] by an X-ray crystal structure analysis (Figure 5). The open-book effect in **6** then directs the gold catalyst to the *exo* face of the enol ether and thus the intermolecular attack of the nucleophile to form hemi-acetal/-aminal **II** by a hydrohydroxylation or hydroamination occurs from the *endo* face. Another, now intramolecular hydroalkoxylation or hydroamination of the in-

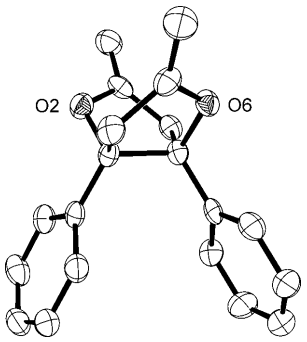


Figure 5. Solid-state molecular structure of **6**.

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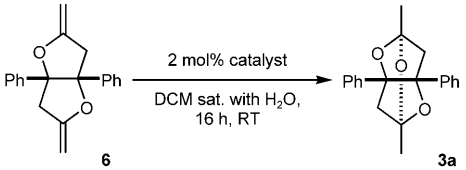
corporated nucleophile finally delivers tricyclic products as single diastereomers. To ensure that intermediate **6** is not only a side product, isolated **6** was re-subjected to the reaction conditions (Table 6). Although Cat A led to complete

Table 6. Conversion of isolated intermediate **6** with H_2O.

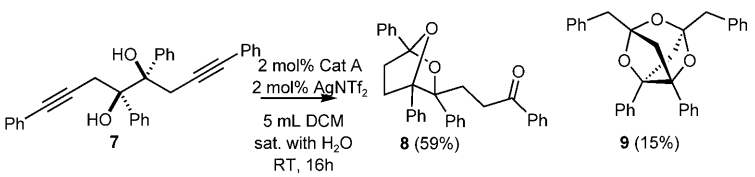


Entry	Catalyst	Result
1	Cat A	complete conversion to **3a**
2	*p*-TsOH	decomposition of the starting material
3	–	no conversion

formation of **3a**, decomposition was observed with *para*-toluenesulfonic acid[15] and no conversion took place in the absence of any catalyst. This stresses the fact that not only the additions to the alkynes, but also the additions to the enol ether substructures of the intermediates are only efficient and selective if converted under the mild conditions of gold catalysis.

Additional proof for the importance of terminal alkynes for the reaction was obtained by the conversion of non-terminal diyne–diol **7**, which was easily available by a Sonogashira coupling. In this case two products were obtained: the tricyclic ketals **9**, and acetal formation and subsequent water addition delivered product **8** (Scheme 5). Both structural assignments could be verified by the results of a crystal structure analysis (Figure 6 and Figure 7).

The selectivity-determining step of the reaction is most probably the initial attack of the tethered oxygen, which in the non-terminal case delivers intermediates **III** and **IV** derived from a 5-*exo-dig* or 6-*endo-dig*[16] cyclisation (Scheme 6). Intermediate **III** now once again favours the 5-*exo-dig* process versus the 4-*exo-trig* enol ether attack, which results in the formation of product **9**. In the case of intermediate **VI**, the distance between the enol ether part and the hydroxyl group enables the nucleophilic attack of the hydroxyl group at the more reactive enol ether part, and no 6-*endo-dig* or 5-*exo-dig* attack at the alkyne takes place in this intramolecular competition. Finally, water attacks at the remaining alkyne and delivers product **8**.



Scheme 5. Reaction of non-terminal alkynes.

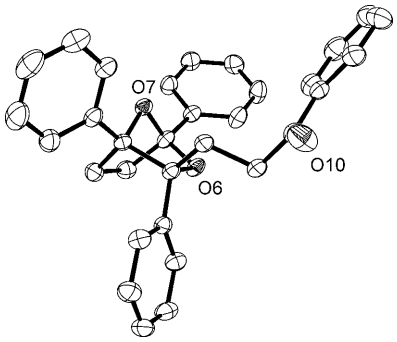


Figure 6. Solid-state molecular structure of **8**.

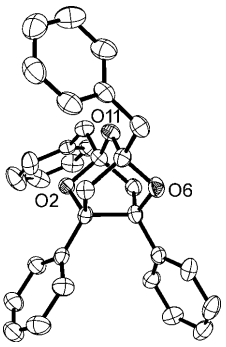


Figure 7. Solid-state molecular structure of **9**.

Conclusion

Readily available *syn*-diyne–diols *syn*-**2** with adequate tether length provide an easy and highly selective access to highly reactive double enol ether intermediates upon subjection to the new NAC-gold catalysts. In a domino cyclisation process, various functionalised intermolecular nucleophiles can be incorporated in these open-book-like structures, finally leading to extremely rigid cage-like assembly in a highly selective reaction. By using the orthogonality of gold and palladium, a subsequent cross-coupling of the resulting tricycles could be demonstrated. To get an impression of the rigidity of the framework created by this methodology, Figure 8 shows a superimposition of two representative examples of the new substrate class. In these geometrically very similar structures, only a slight torsion of the attached aromatic moieties is visible. The incorporation of other types of nucleophiles and further variations of the starting diyne–diols, for example, by introduction of functional groups for cross-coupling reactions orthogonal to the gold-catalysis are under investigation and will be published in due course. Especially the use as a core group in material science, placing electronically/photochemically active π systems at well-defined distances is a focus of these efforts.

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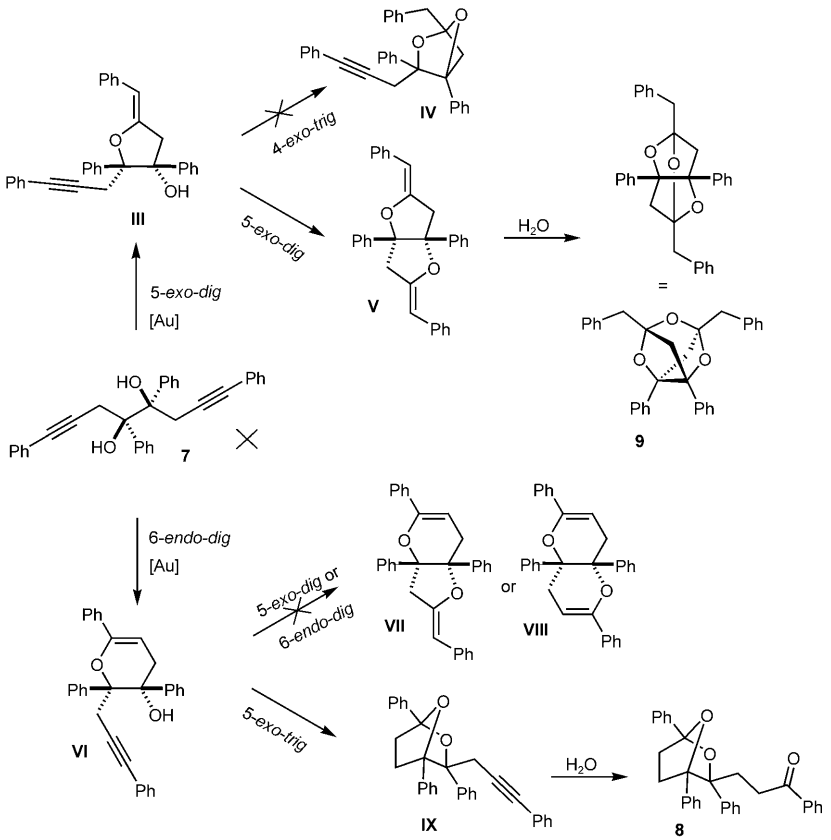

Scheme 6. Mechanistic considerations for the formation of **8** and **9**.

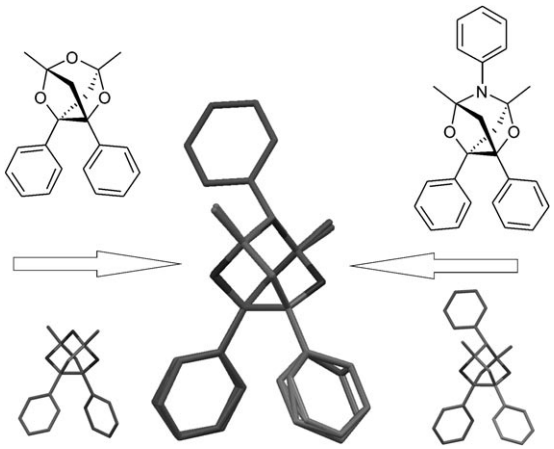

Figure 8. Superimposition of representative solid-state molecular structures of one trioxa- and one azadioxa-tricycle.

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