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Gold-Catalyzed Synthesis of Chroman, Dihydrobenzofuran, Dihydroindole, and Tetrahydroquinoline Derivatives

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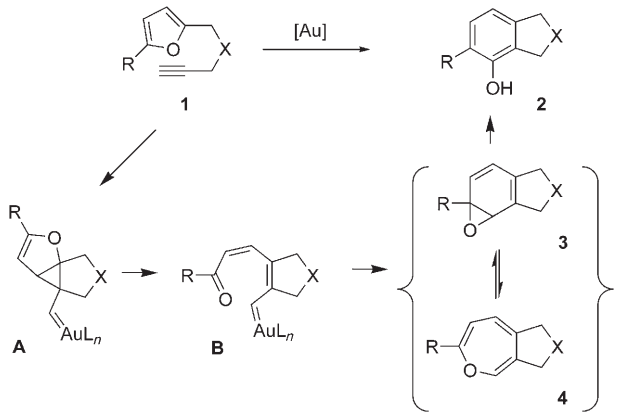
Abstract: Different furans containing an ynamide or alkynyl ether moiety in the side chain were prepared. The gold-catalyzed transformation of these compounds delivered dihydroindole, dihydrobenzofuran, chroman, and tetrahydroquinoline derivatives at room temperature through very fast reactions. Furthermore, the stabilizing effect of the heteroatom directly attached to the intermediate arene oxides led to highly selective reactions, even in the case of only mono-substituted furans, which is quite different from previous results obtained with non-heteroatom-substituted alkynes.

Keywords: alkynes · arenes · gold · heterocycles · homogeneous catalysis

Introduction

The importance of gold catalysis as a powerful tool for organic synthesis is continuously increasing;[1] the cyclization of enynes is playing a major role.[2a,b] In our group, we developed a gold-catalyzed phenol synthesis (Scheme 1), in which the first step, like all the other ene–yne cyclizations, probably involves a cyclopropyl carbenoid (**A**) or an electronically related structure, but then due to the additional enol ether substructure follows a different pathway (via **B** and the valence tautomers **3**/**4**) to ultimately form the aromatic phenols **2**.[3] This methodology has proven to be a powerful tool for the synthesis of various heterocycles, such as dihydroisoindoles,[3a–c,f,h,i,k,l] tetrahydroisoquinolines,[3a,f,i–l,n] dihydroisobenzofurans,[3a,m] and isochromans.[3m] All of these heterocycle syntheses are based on a propargylic moiety connected to the heteroatom in the tether of the substrate **1**. Herein, we report on our efforts to use alkynyl moieties directly connected to the heteroatom as reactive units in the side chain of the furans, namely alkynyl amides and alkynyl ethers. This should provide access to other types of heterocycles, such as dihydroindoles, dihydrobenzofurans, chromans, and tetrahydroquinolines.



Scheme 1. Gold-catalyzed phenol synthesis.

So far only very few examples of the gold-catalyzed ene–ynamide[4a] and ene–ynol ether[5] cyclizations have been reported. The gold-catalyzed cyclization of 1,6-ene–ynamides **5** developed by Cossy et al. delivered cyclobutanones **6** as

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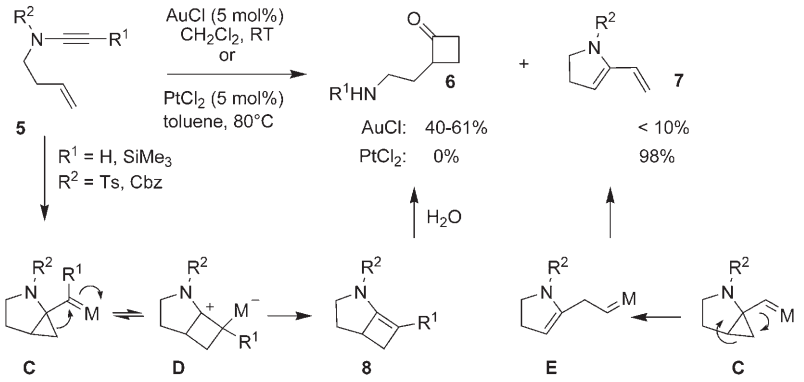
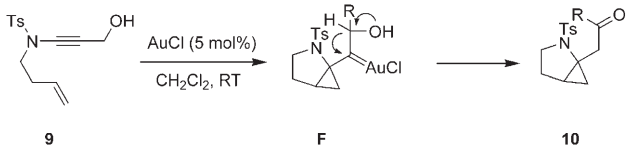


Scheme 2. Pathways for metal-catalyzed enyne cyclization of ynamides. Ts = tosyl; Cbz = benzyloxycarbonyl.

major products,[4a] whereas similar substrates in platinum-catalyzed reactions delivered exclusively formal metathesis products **7** (Scheme 2).[4b,c] The different chemoselectivity can be explained by the milder reaction conditions of the gold-catalyzed reactions. Here a ring expansion of the primary cyclopropyl carbenoid **C**, leads to a cyclobutyl cation **D** (stabilized by the neighbouring heteroatom). After elimination of the metal and addition of water to cyclobutene **8**, products **6** are formed. A double cleavage of the primary carbenoid complex **C** in the platinum-catalyzed reaction delivers carbenoid **E**, which finally results in products **7** after elimination of the metal.

By the use of substrate **9**, which contains a propargylic alcohol moiety, the cyclopropyl carbenoid **F** could be trapped by a 1,2-hydride shift to deliver the ketone **10** (Scheme 3).[4]



Scheme 3. A third pathway for gold-catalyzed enyne cyclization of ynamides.

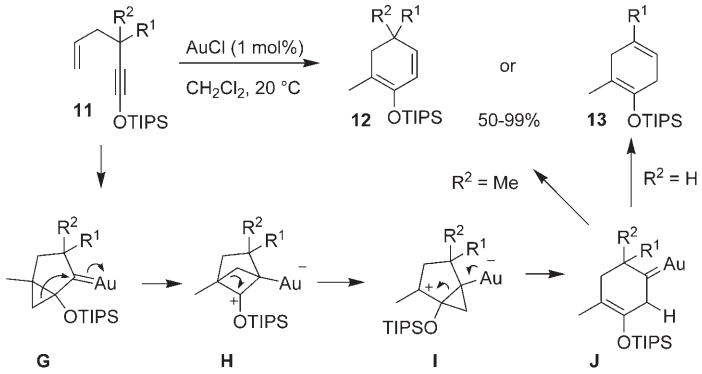
The products formed by the gold-catalyzed cyclization of siloxy enynes **11**, reported by Kozmin et al.,[5] are also influenced by a stabilizing effect of the attached heteroatom. After the initial formation of the cyclopropylcarbenoid **G**, ring expansion, leading to cyclobutyl cations **H**, and a subsequent skeletal rearrangement via **I** to carbenoid **J**, could explain the shift of the silyl ether group in the final products **12** or **13** (depending on the substitution pattern, Scheme 4).

Results and Discussion

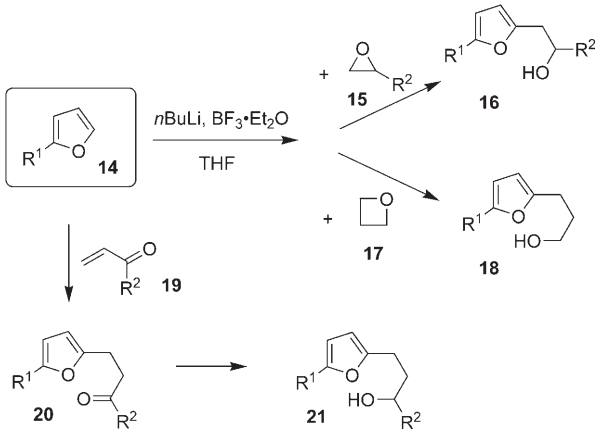
The introduction of the side chain for the dihydrobenzofuran syntheses was achieved by the addition of lithiated furans **14** to oxiranes **15**.[3m] The corresponding three-carbon-atom chain for chroman synthesis was introduced by Michael addition of furans **14** to enones **19** and subsequent reduction of the carbonyl group of **20** to the alcohol **21**.[6–8] Alternatively, a boron trifluoride etherate mediated addition of lithiated furan to oxetane **17** provided direct access to the alcohol **18** in good yield (Scheme 5).[9]

The resulting alcohols **16**, **18** and **21** were transformed into the dichlorovinyl ethers **23a–d** (Table 1) by following a protocol of Greene et al.[10] The addition of the alcohols to trichloroethene in THF provided **23a–d** in yields of 66–80%. The addition of decanol (**22**) to trichloroethene yielded the alkyl vinyl ether **23e** in 70% yield.

The starting points for the ynamide syntheses were the toluenesulfonamides **24a–d** (Table 2), which were prepared by literature procedures from the corresponding amines.[3l,n] Toluenesulfonamides **24e**/**24g**, containing a three-carbon-atom unit were synthesized from the corresponding alcohols

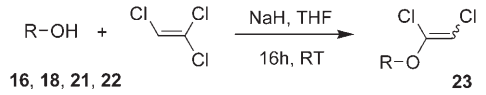


Scheme 4. Reactions of alkynyl ethers in gold-catalyzed reactions. TIPS = triisopropylsilyl.



Scheme 5. Synthesis of furans with hydroxy groups in the side chain.

Table 1. Formation of the dichlorovinyl ethers **23**.



16, **18**, **21**, **22** **23**

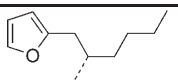
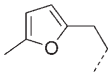
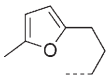
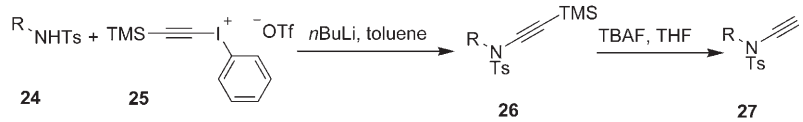
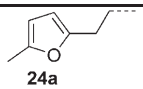
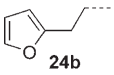
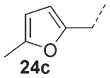
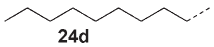
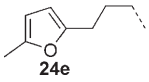
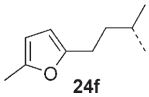
Entry	**16**,**18**,**21**	R	Product (yield [%])
1	**16a**		**23a** (79)
2	**16b**		**23b** (80)
3	**18a**		**23c** (66)
4	**21a**		**23d** (75)
5	**22**		**23e** (70)

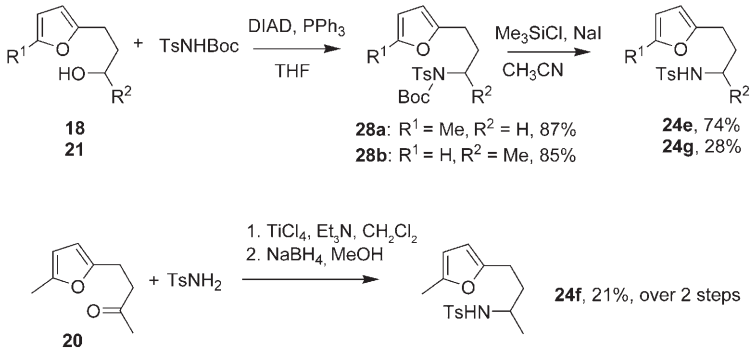
Table 2. Synthesis of compounds **27** via alkynyliodonium salts.[a]



24 **25** **26** **27**

Entry	R	Reaction time	**26** (yield [%])	yield of **27** ([%])
1	 **24a**	3 d	**26a** (65)	**27a** (100)
2	 **24b**	16 h	**26b** (65)	**27b** (100)
3	 **24c**	16 h	**26c** (43)	**27c** (99)
4	 **24d**	2 d	**26d** (48)	**27d** (99)
5	 **24e**	2 d	slow decomposition	–
6	 **24f**	2 d	slow decomposition	–

[a] TMS = trimethylsilyl; TBAF = tetrabutylammonium fluoride



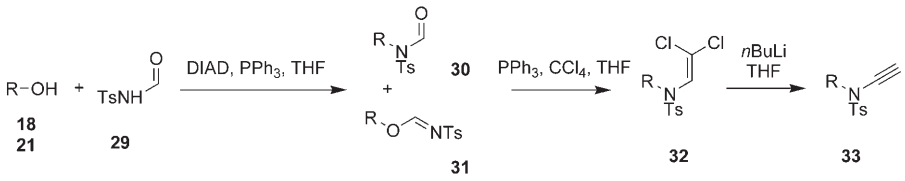
Scheme 6. Different routes to tosylamides **24**. DIAD = diisopropyl azodicarboxylate.

18a/21a by a Mitsunobu reaction with *N*-*tert*-butyloxycarbonyl-*p*-toluenesulfonamide[11] and subsequent deprotection of **28a**/**28b** with trimethylsilyl iodide (Scheme 6).[12] A deprotection under acidic conditions led to decomposition of the starting materials. Alternatively, $TiCl_4$-mediated tosylimine formation and reduction delivered amide **24f** in moderate overall yield (Scheme 6). To introduce the alkyne moiety, we used a procedure published by Witulski's group.[13] Addition of deprotonated amides in toluene to trimethylsilylethynylphenyliodonium triflate[14] **25** and deprotection with tetrabutylammonium fluoride delivered ynamides **27a–d** in moderate overall yields (Table 2). A partial loss of product might result from problems during purification. Unfortunately, amides **24e** and **24f** containing a three-carbon-atom unit did not react—only a slow decomposition could be detected by TLC.

As a consequence, we switched to a protocol of Brückner et al. (Table 3).[15] Our intention was the direct introduction of the tosylated nitrogen under Mitsunobu conditions. The necessary alcohols **28** are easily available. A Mitsunobu reaction of *N*-formyl toluenesulfonamide **29** delivered mixtures of N- and O-alkylated products **30**/**31**, which—without purification—were directly converted to the dichlorovinyl amides **32a–c** in moderate to good overall yields (depending on the steric demand of the alcohols **28**, which led to different N/O ratios of the intermediate products **30** and **31** that were formed by substitution of the ambident formamide nucleophile). Chloride elimination with *n*BuLi led to ynamides **33a–c** in excellent yields.

For the gold-catalyzed formation of oxygen heterocycles we used two different procedures (methods A and B as described in Scheme 7). Elimination to **34** with *t*BuLi at −78 °C delivered cleaner crude alkynyl ethers than elimination with *n*BuLi. The isolated alkynyl ethers **34a–e** were used for gold catalysis without further purification. Both solvents CH_3CN and $CHCl_3$ were suitable for the gold-catalyzed transformations. When CH_3CN was used, a competitive addi-

Table 3. Synthesis of ynamides via *N*-formyl toluenesulfonamides.



Entry	R–OH	R	Reaction time [h]	**32** (yield [%])	**33** (yield [%])
1	**21a**		16	**32a** (21)	**33a** (82)
2	**21b**		16	**32b** (20)	**33b** (90)
3	**18**		48	**32c** (57)	**33c** (98)

tion of water to substrate **34a** finally led to ester **36** as a side product. All reactions proceeded nicely and very quickly at room temperature with 3–5 mol% $AuCl_3$. The XRD analysis of dihydrobenzofuran **35b** (Figure 1) shows two independent molecules with rather similar dimensions.[16] The molecules are connected by intermolecular hydrogen bonds in zig-zag chains, which are also stabilized by C–H–π interactions. Remarkably, the unsubstituted furans **34a** and **34d** reacted selectively as well; the oxygen atom directly attached to the intermediate arene oxides **28** led to a selective ring opening; this is in accord with our recent studies on the mechanism, which indicated that the substrate and not the catalyst determine the selectivity of the last step, the opening of the intermediate arene oxide (Scheme 8).[17] The position of the oxygen atom could be proven by XRD analysis. Figure 2 shows the four independent conformers of the elemental cell of a single crystal of **35d** together with two water molecules. The corresponding furans with propargylic heteroatoms in the tether always delivered a mixture of constitutional isomers.[3a] Unfortunately, efforts to achieve an intermolecular reaction of substrate **34e**, analogous to previously reported results, with 2,5-dimethylfuran were unsuccessful (Scheme 9).[18]

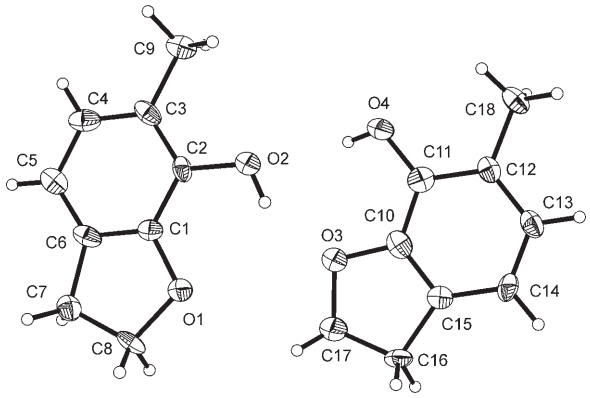
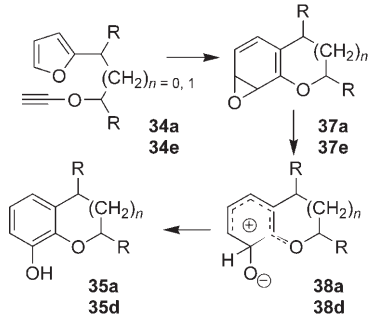
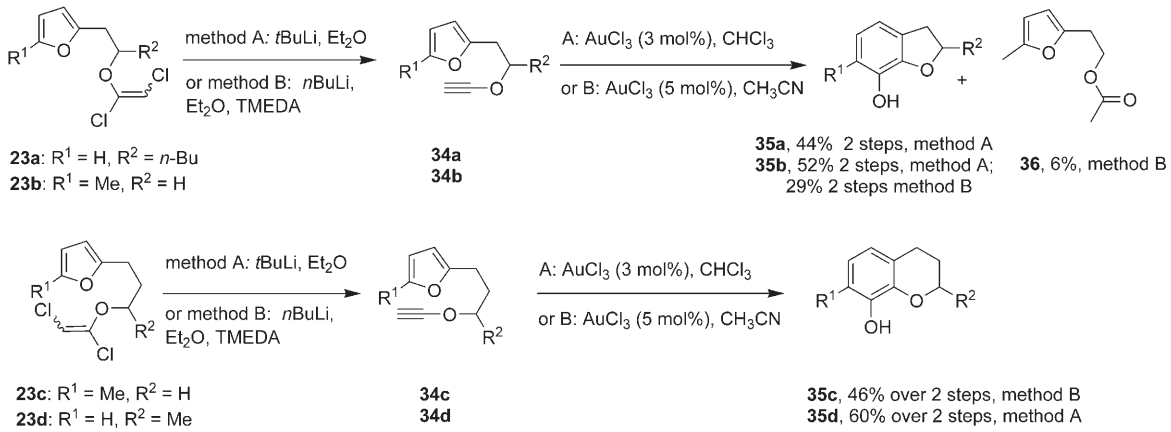


Figure 1. Solid state structure of **35b**.



Scheme 8. The influence of the alkoxy substituent on the ring opening of the arene oxides.



Scheme 7. Synthesis and gold-catalyzed conversions of the alkynyl ethers. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

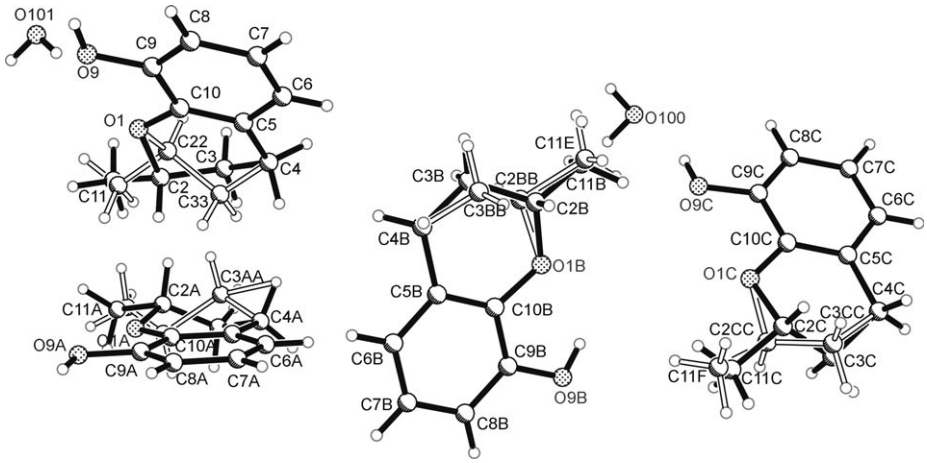
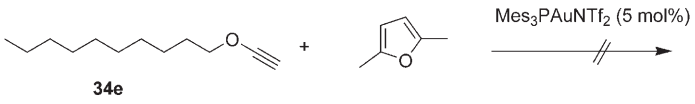


Figure 2. Solid state structure of **35d**.



34e

Scheme 9. No efficient intermolecular phenol synthesis was observed with the alkynyl ether **3e**. Mes = mesityl; Tf = triflate.

The gold-catalyzed dihydroindole formation with substituted furan **27a** delivered the product **39a** in good yield and with a very short reaction time (short reaction time relative to other substrates in the phenol synthesis in which a heteroatom is not directly attached to the alkyne, Table 4) by using 5 mol% $AuCl_3$ as the catalyst. Single crystals for XRD analysis could be obtained (Figure 3). An intramolecular hydrogen bond between the phenolic hydrogen atom and the oxygen atom is observed. Problems occurred for unsubstituted substrate **27b**. In this case, the reaction was very unselective for gold(I) complexes and only the pyridine–gold(III) complexes **40**[19] and **41** delivered a small amount of product **39b**. During preparation of complex **41**, single crystals were also obtained. The X-ray crystal structure (Figure 4) shows the typical square-planar surroundings of the gold atom.

Tetrahydroquinolines **42b** and **42c** were formed very quickly and in good to excellent yields from **33b**/**33c** with $AuCl_3$ in $CHCl_3$. In comparison to earlier studies for the formation of benzo-anellated six-membered rings in the phenol synthesis, the reaction times here are much shorter. Again, the unsubstituted furan **33a** delivered a lower yield of **42a**. Once more, the yield of **42a** could be improved by switching to pyridine complexes **40** and **41** (Table 5) in CD_3CN. Fortunately, single crystals for **42a** could be obtained. The X-ray crystal structure (Figure 5) unambiguously shows the position of the oxygen atom at the 8-position of the tetrahydroquinoline structure. Two intermolecular hydrogen bonds between the phenolic hydroxyl group and the oxygen atom of the tosyl group are observed. The X-ray crystal structure of product **42b** shows two different conformers, which are stabilized by two intermolecular hydrogen bonds (Figure 6). Compound **42c** also gave crystals suitable for XRD analysis

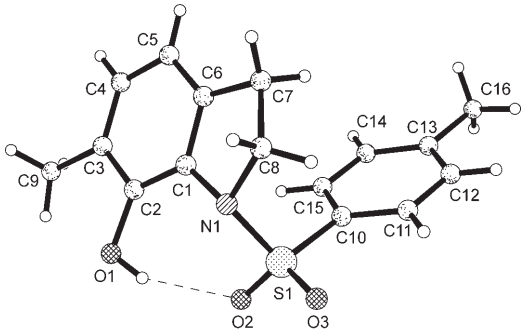


Figure 3. Solid state structure of **39a**.

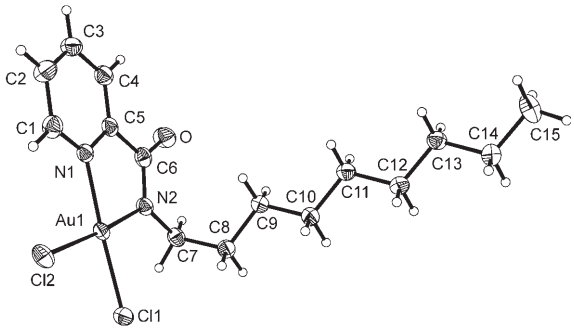
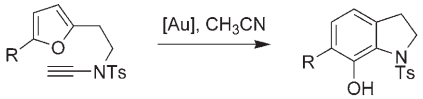


Figure 4. Solid state structure of catalyst **41**.

Table 4. Gold-catalyzed conversion of the ynamines **27**.



27a: R = Me
27b: R = H

39a
39b

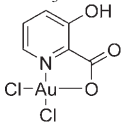
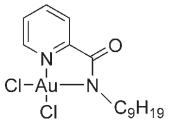
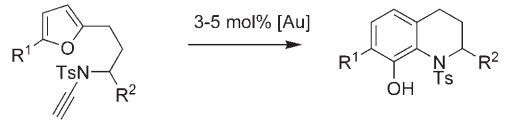
Entry	**27**	Catalyst	Loading [mol%]	Reaction time	**39** (yield [%])
1	**27a**	$AuCl_3$	5	5 min	**39a** (62)
2	**27b**		3	5 min	**39b** (13)
3	**27b**		3	1 h	**39b** (9)

Table 5. Gold-catalyzed conversion of the ynamines **33**.



33a: R^1 = H, R^2 = Me
33b: R^1 = Me, R^2 = Me
33c: R^1 = Me, R^2 = H

42a
42b
42c

Entry	**33**	Catalyst	Loading [mol%]	*T* [°C]	Solvent	Reaction time	**42** (yield [%])
1	**33a**	$AuCl_3$	3	0	$CDCl_3$	5 min	**42a** (17)
2	**33a**	**40**	5	RT	CD_3CN	1 h	**42a** (26)
3	**33a**	**41**	5	RT	CD_3CN	16 h	**42a** (37)
4	**33b**	$AuCl_3$	3	0	$CDCl_3$	5 min	**42a** (88)
5	**33c**	$AuCl_3$	3	0	$CDCl_3$	5 min	**42a** (67)

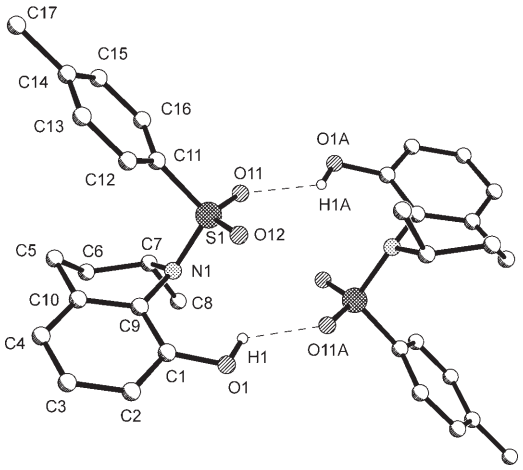


Figure 5. Solid state structure of product **42a**.

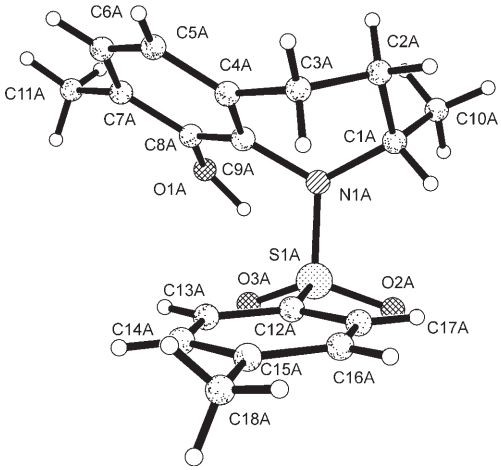


Figure 6. Solid state structure of product **42b**.

(Figure 7). The molecule shows an intramolecular hydrogen bond between the phenolic hydrogen atom and the oxygen atom of the tosyl group. The intermolecular reaction of **27d** with dimethylfuran turned out to be unselective

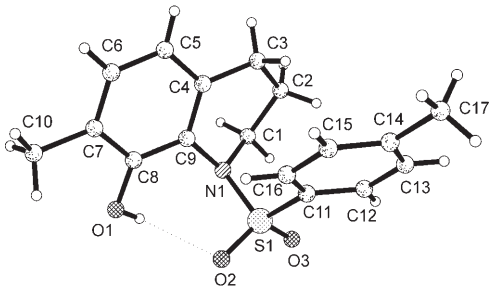
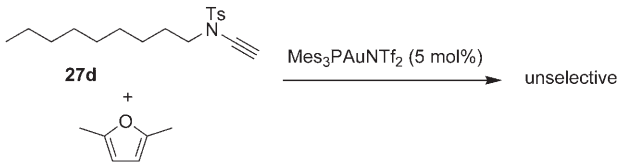


Figure 7. Solid state structure of product **42c**.

(Scheme 10). Compound **27c**, with only one carbon atom in the side chain, also did not produce a selective reaction.



Scheme 10. No selective intermolecular phenol synthesis was observed with **27d**.

Conclusion

The routes presented here, allow an efficient access to chromans, dihydrobenzofurans, dihydroindoles, and tetrahydroquinolines from furans by two simple steps and a subsequent gold-catalyzed reaction of the substrates containing an ynamide and ynol ether moiety in the side chain. In contrary to the reported gold-catalyzed reactions, no ring expansion of the primary cyclopropyl carbenoids could be observed. This indicates a very fast ring opening of the strained cyclopropyl carbenoid **A**, to form the monocyclic carbenoid **B**. Furthermore, due to the stabilizing effect of the heteroatom, which was directly attached to the intermediate pentadienyl cation, selectivity problems were not observed for unsubstituted furans. Relative to other, previously described substrate types for the phenol synthesis, the donor-substituted alkynes reacted very quickly.

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