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New pathways in the gold-catalyzed cycloisomerization of furanynes*

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Abstract: The most familiar gold-catalyzed cyclization pathway for furanyne substrates leads to synthesis of phenols, but new reaction pathways have recently been discovered. The mechanistic background and the synthetic possibilities of these alternative pathways leading to new heterocyclic products are discussed.

Keywords: alkynes; alkynyl amides; alkynyl ethers; arenes; gold; heterocycles; transition-metal-catalyzed reactions.

INTRODUCTION

During the past decade, the status of homogeneous gold catalysis has risen from an exotic topic to a reliable tool for organic synthesis. Earlier work by Ito, Sawarmura, and Hayashi [1] as well as by Utimoto et al. [2] and Teles et al. [3] somehow failed to stimulate a broader interest in the field at that time. The turning point was in the year 2000, when two papers [4,5], which were then highlighted [6–8] in the literature and have since become well cited, triggered enormous interest in homogeneous gold catalysis, which continues to show exponential growth [9]. Numerous reviews summarize the unique and creative innovations of almost 100 groups world-wide [10–20]. Most of these gold-catalyzed reactions proceed under very mild conditions and are atom-economic.

The most important reactivity pattern is the activation of a C–C multiple bond for the attack of a nucleophile. In the case of furanyne cyclization [5], the C–C triple bond of a pendant alkynyl group is activated and the furan ring serves as an intramolecular nucleophile.

GOLD-CATALYZED PHENOL SYNTHESIS

Furanyne cyclization leading to phenol synthesis is probably the gold-catalyzed reaction that offers the broadest scope in synthesis, and has a record of being highly reliable. As shown in Scheme 1, this reaction allows the synthesis of a range of different benzo-annelated carbo- and heterocycles. The illustrated examples demonstrate that even sterically demanding substituents like the adamantyl group or the mesityl group are tolerated, as well as the presence of nitrogen and oxygen atoms in the tether. A whole series of publications has emanated from this reaction pathway [21–36]. A crucial synthetic advantage of the method is the location of the phenolic hydroxy group *ortho*- to the ring-junction in the annelated product. This selectivity is difficult to achieve by traditional annelation methods, owing to competing pathways arising from activation of the aromatic ring at both the *ortho*- and *para*-positions in conven-

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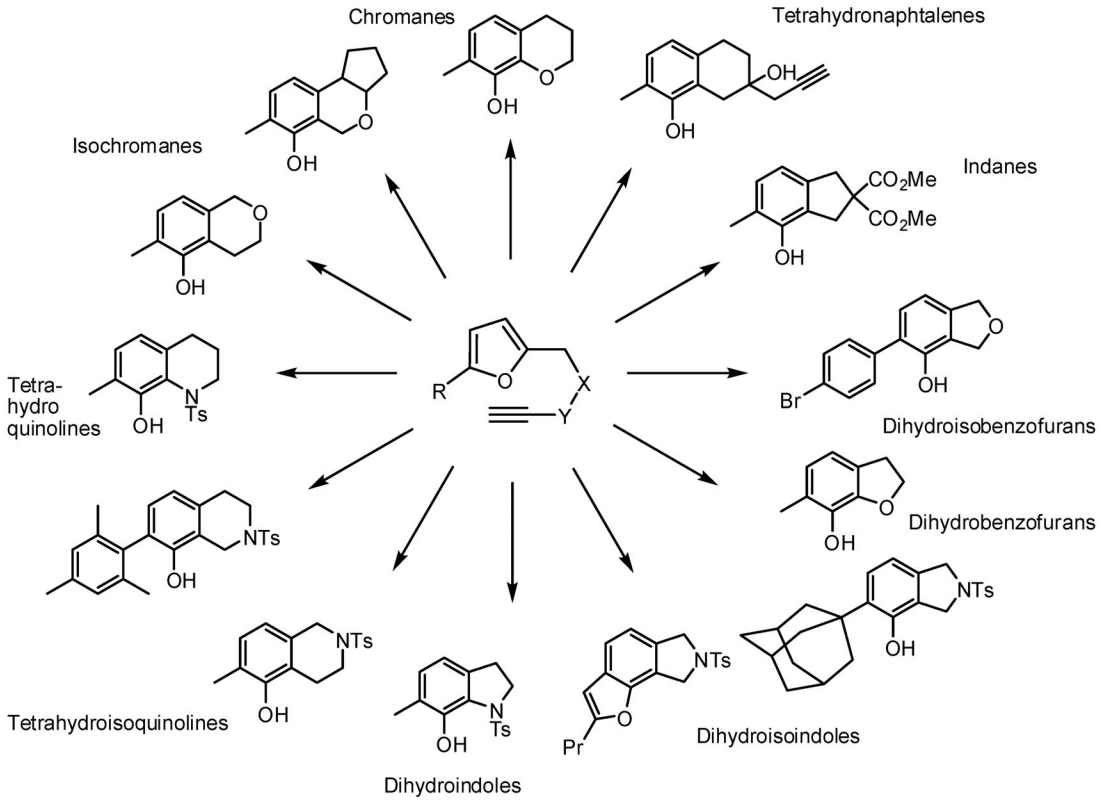
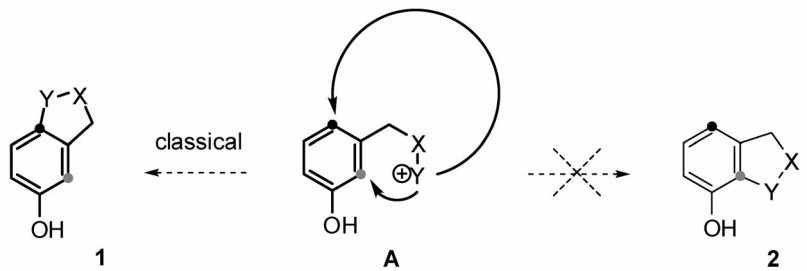
tional phenolic reactants (Scheme 2). Due to steric repulsion, an electrophilic intermediate generated in situ (**A**) attacks the phenol preferentially in the *para*-position to deliver **1** rather than in the *ortho*-position to provide **2**, like in the Pictet–Spengler reaction [37,38]. Furthermore, apart from selectively reaching a difficult substitution pattern not easily accessible by other methods, this hydroxy group can be further modified. For example, it can be transformed to aryl triflates [29] and the C–O bond be converted to a C–C bond by a subsequent cross-coupling.

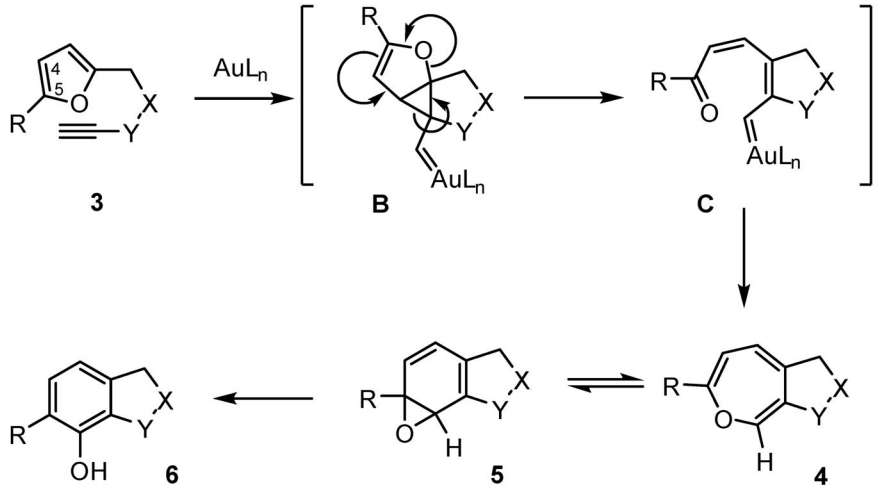


Scheme 1 Gold-catalyzed cycloisomerization of *N*-propargyl carboxamides (X-Y = CR_2CR_2, $CR_2CR_2CR_2$, O CR_2, CR_2O, $NRCR_2$, CR_2NR, $NRCR_2CR_2$, CR_2NRCR_2, CR_2CR_2NR, OCR_2CR_2, CR_2OCR_2, CR_2CR_2O).



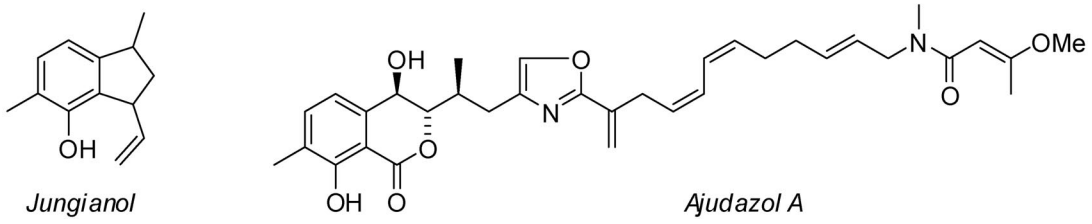
Scheme 2 Classical annelation methods do not favor location of the hydroxy group *ortho*- to the annelation point (e.g., Pictet–Spengler reaction, X-Y = $CR_2N^+(H)$=CHR).

Mechanistically, gold-catalyzed cycloisomerization of furanynes are well understood. Scheme 3 shows the reaction pathway based on today's knowledge. Starting from the furanyne **3**, gold coordinates the triple bond and then initiates cyclization leading to a cyclopropyl carbenoid **B**. This opens up to the vinyl carbenoid **C**. Nucleophilic attack of the carbonyl oxygen atom of **C** and elimination of gold then leads to the oxepine intermediate **4**, which has been detected by in situ NMR spectroscopy [30]. This intermediate **4** is in a valence tautomeric equilibrium with the arene oxide **5**, which has also been identified by in situ NMR spectroscopy and can be trapped by Diels–Alder reactions [28]. Finally, opening of the oxirane ring in **5** and aromatization leads to the phenol **6**. The regioselectivity of epoxide ring opening is controlled by substituents on the cyclohexadienyl cation intermediate [36]. Thus, a donor substituent (R = alkyl, aryl, alkynyl) on the 5-position of the furan ring of **3** always leads to the substitution pattern shown in **6**, but the alternative isomer is also obtained in the absence of any 5-substituent (R = H). No conversion is observed with acceptors in the 5-position (e.g., R = CO_2R), but weak acceptors in the 4-position are tolerated.



Scheme 3 Mechanism of the gold-catalyzed phenol synthesis (X-Y specified as in Scheme 1).

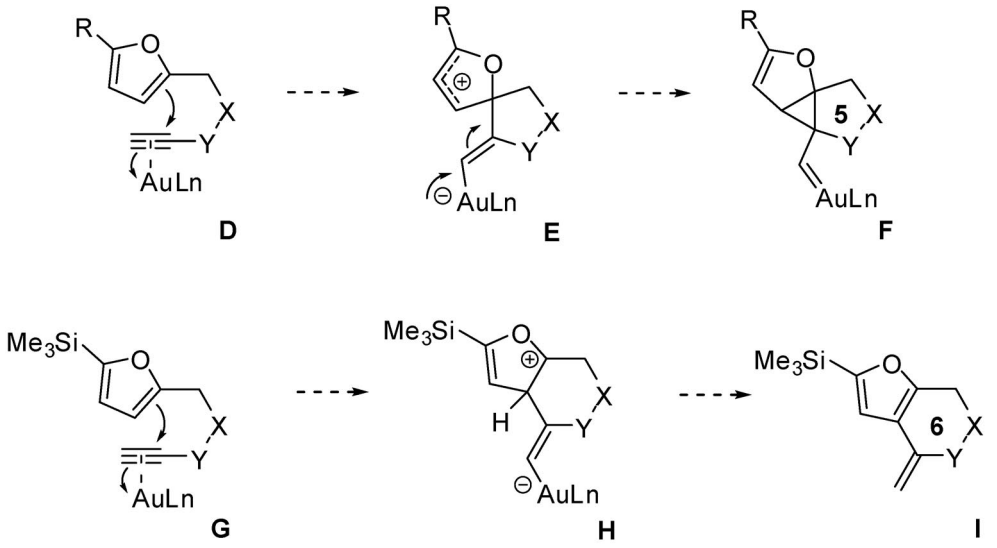
The gold-catalyzed phenol synthesis has found applications in total synthesis of the natural product *jungianol* [25,39,40] (Scheme 4), and in current studies toward the synthesis of *ajudazols* [41,42].



Scheme 4 The natural products *Jungianol* and *Ajudazole* are target molecules with the gold-catalyzed phenol synthesis as a potential key reaction.

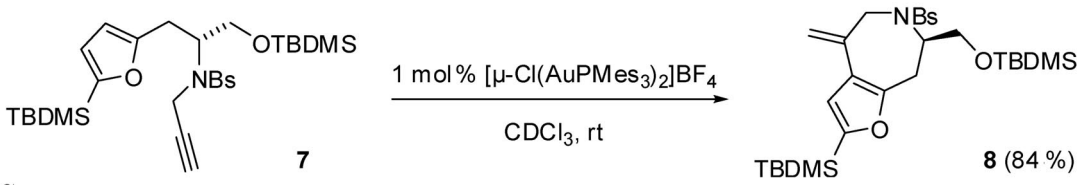
SWITCHING FROM THE PHENOL SYNTHESIS TO INTRAMOLECULAR HYDROARYLATION

When a silyl group is placed on the 5-position of the furan ring, the most nucleophilic position of the furan ring changes. Now the β-position to oxygen is more nucleophilic than the α-position (a similar effect is known from pyrrolynes in gold-catalyzed conversions, even with a tosyl group on nitrogen the β-position to nitrogen is more nucleophilic and only hydroarylation chemistry is observed [29]). In the phenol synthesis, the conversion of **3** to intermediate **B** could be interpreted to be a step-wise process with an intial attack at the 2-position of the furan ring of **D**, closing a five-membered ring in **E** and **F** by a 5-*exo-dig* cyclization (Scheme 5). With a silyl group on the furan ring as in **G**, a six-membered ring in **H** and **I** should be formed by a 6-*endo-dig* cyclization.



Scheme 5 A silylation of the 5-position of the furan ring should change the regioselectivity at the furan ring; in the phenol synthesis intermediates **E/F** are formed, with the silylated furans the intermediate **H** would deliver hydroarylation products **I** (X-Y = CR_2NRCR_2).

As expected, the silyl group allowed the synthesis of unique furo-annelated heterocycles, even the seven-membered ring in **8** could be formed in good yield (Scheme 6). A dinuclear gold(I) precatalyst was used for this conversion. In the case of the products **9** and **10**, the additional five-membered oxazolidinone ring due to geometrical restraints during the ring-closure (the five-membered oxazolidinone widens the angles in the tether, the distance between the reacting units increases) did not facilitate ring-closure and much lower yields were obtained (Fig. 1).



Scheme 6 The silylated substrate **7** indeed delivered furo-annelated seven-membered rings by hydroarylation.

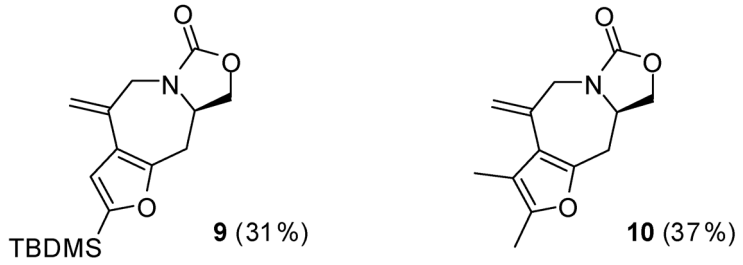
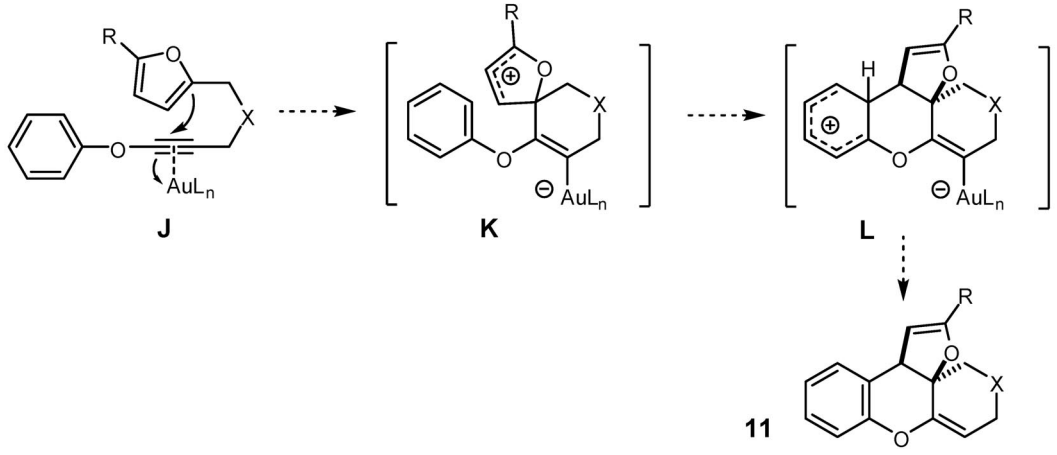


Fig. 1 Reduced yields were observed in the case of silylated furanynes with oxazolidinone rings in the tether.

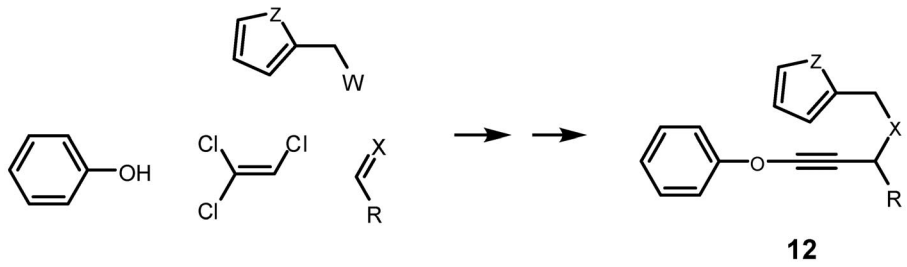
SWITCHING FROM THE PHENOL SYNTHESIS TO TETRACYCLIC HETEROCYCLES BY ARYLOXY GROUPS ON THE ALKYNE

Placing new substituents on the alkyne rather than on the furan ring led to new product types. As described above for intermediates like **B**, **E**, and **H** (Scheme 5), the gold usually is placed at the terminal (distal) position of the alkynyl group. The presence of an oxygen donor atom in intermediate **J** would change the polarity of the alkyne, due to a polarization similar to an enol-ether, the electrophilic gold catalyst would now get attached to the other (proximal) end of the alkyne, now closing a six-membered ring by an 6-*endo-dig* cyclization to the 2-position of the furan ring in intermediate **K**. In **K** the electrophilic carbon at the 3-position of the furan ring could easily attack the neighboring aryl group to form **L**, which then by re-aromatization and protodeauration would deliver **11** (Scheme 7).



Scheme 7 An aryloxy group on the alkyne should change the regioselectivity at the alkyne. By an initial 6-*endo-dig* cyclization and electrophilic substitution heteropolycycles **11** should be obtained (X = NR; R = H).

In order to be an interesting synthetic method, the synthesis of the starting materials **12** needed to be simple and efficient. By a one-pot procedure this was accomplished; the cheap building blocks shown in Scheme 8, a phenol, trichloroethene, an aldehyde or an aldimine and a furan derivative deliver **12**. This modular access to the substrates even allows the synthesis of libraries of substrates **12** by variation of the components.



Scheme 8 A short sequence delivers the substrates **12** (W = leaving group; X = NR'; Z = O, NR, S; R = alkyl).

With these substrates we could test the hypothesis, and indeed the expected polycyclization was accomplished. Some examples of the products obtained by the conversion of different substrates are shown in Fig. 2 [43]. With stereocenters in the substrate, even a 1,4-induction was possible, a methyl group in **17** led to a 71:29 ratio of diastereomers, the more bulky ethyl in **14** group improved the d.r. to 90:10. We were delighted that even pyrroles (to **18** and **19**) and thiophenes (**20**) react the same way, two classes of heterocyclic substrates which never gave satisfactory results in the gold-catalyzed phenol synthesis. The constitution of the products was proven unambiguously by several crystal structure analyses (two examples shown in Fig. 3). The two structures nicely demonstrate the dearomatization of the heterocycle, forming the new stereocenter at the position labeled C-2.

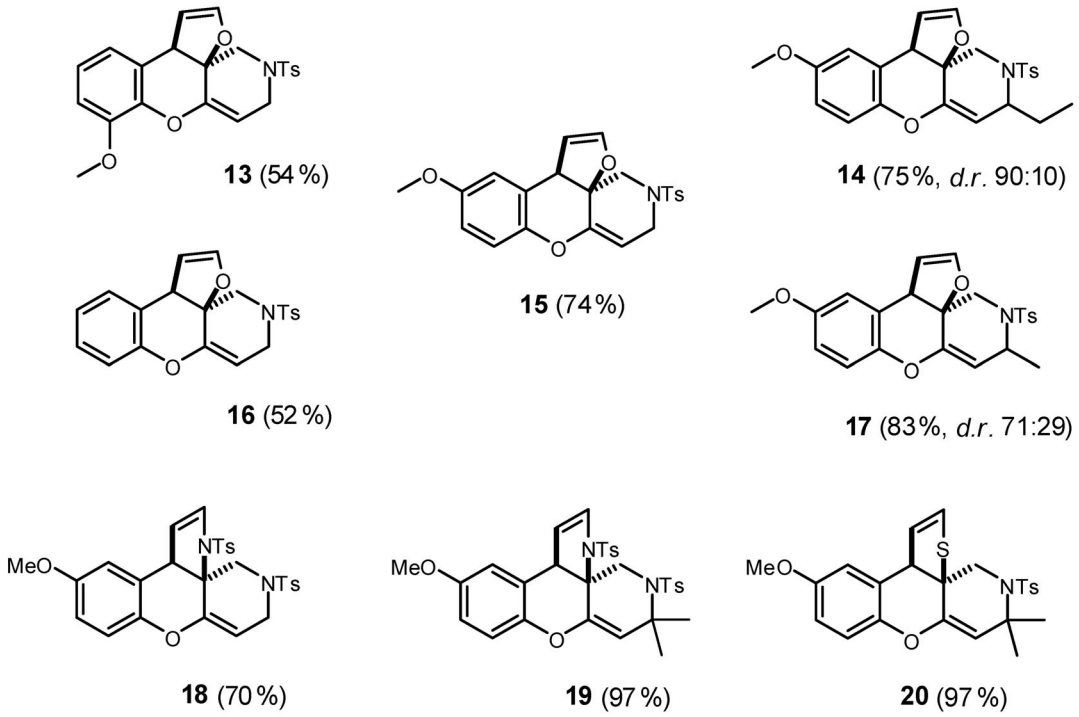
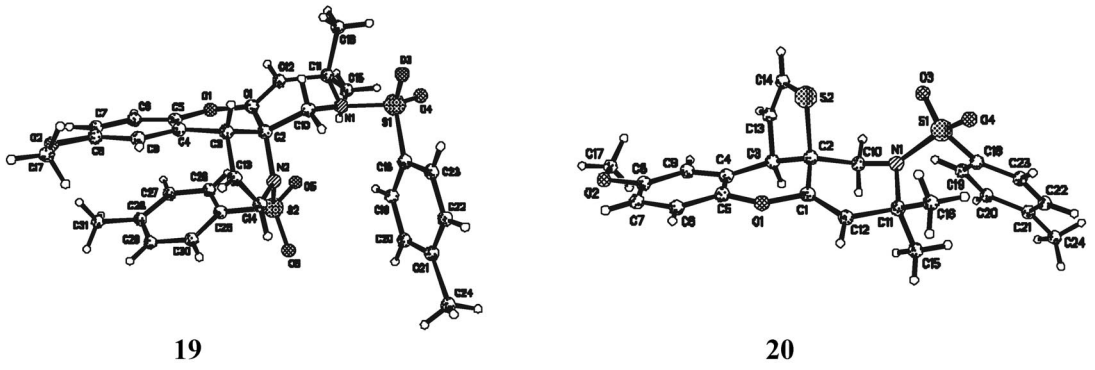


Fig. 2 Hetero-polycyclic products obtained by the gold-catalyzed conversion of substrate of type **12**.

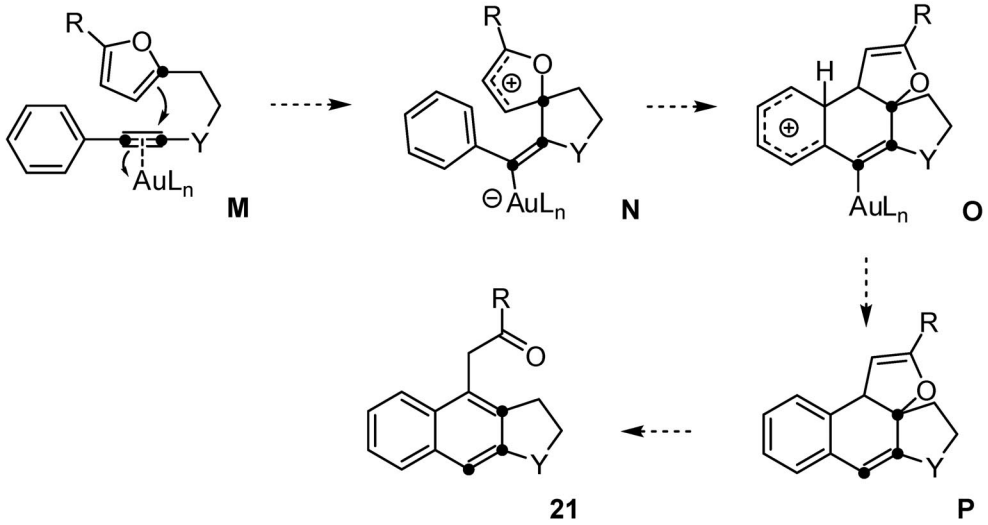


19 **20**

Fig. 3 Solid-state structures of the products **19** and **20**, clearly proving the product connectivity also for pyrrole- and thiophene-based substrates.

SWITCHING FROM THE PHENOL SYNTHESIS TO AN ARYL GROUP AT THE DISTAL AND A DONOR GROUP AT THE PROXIMAL END OF THE ALKYNE

The next change we intended to investigate was to place the aryl group at the distal and the heteroatom tether at the proximal end of the alkyne. The donor should now direct the gold catalyst to the end of the phenyl group, initiating a 5-*exo-dig* ring closure from **M** to **N**. Since the nucleophile attacks the activated triple bond from the back side, the phenyl group and the cation should be on the same side of the double bond of the vinylgold intermediate **N**, thus a second ring could close to form **O**. Re-aromatization of the phenyl group and protodeauration could deliver **P**, since elimination of the oxygen tether at the central ring now would cause an aromatization of the latter, **21** is expected as the final product (Scheme 9).



Scheme 9 Expected pathway, a 5-*exo-dig* cyclization, electrophilic substitution and elimination to deliver product **21** (Y = NR'; R = alkyl).

This methodology could be applied quite successfully. The products shown in Fig. 4 were prepared that way [44]. Apart from a number of substrates with phenyl groups (leading to **22**, **23**, **27**, and

30), also naphthyl groups (leading to **24** and **31**), furan (**25**), benzofuran (**32**), indole, and even thiophenes (leading to **28** and **29**) were tolerated. This demonstrates the possibilities in the synthesis of different types of heterocycles. The structures were confirmed by crystal structure analyses. Figure 5 shows compound **28** as one example, one can nicely see the penta-substituted central core which is annelated to two different heterocyclic rings and the ketone in the side chain, potentially allowing further annelation or functionalization. This underlines the importance of the crystal structure analysis in this field, a safe assignment only by NMR spectroscopy would not have been easy.

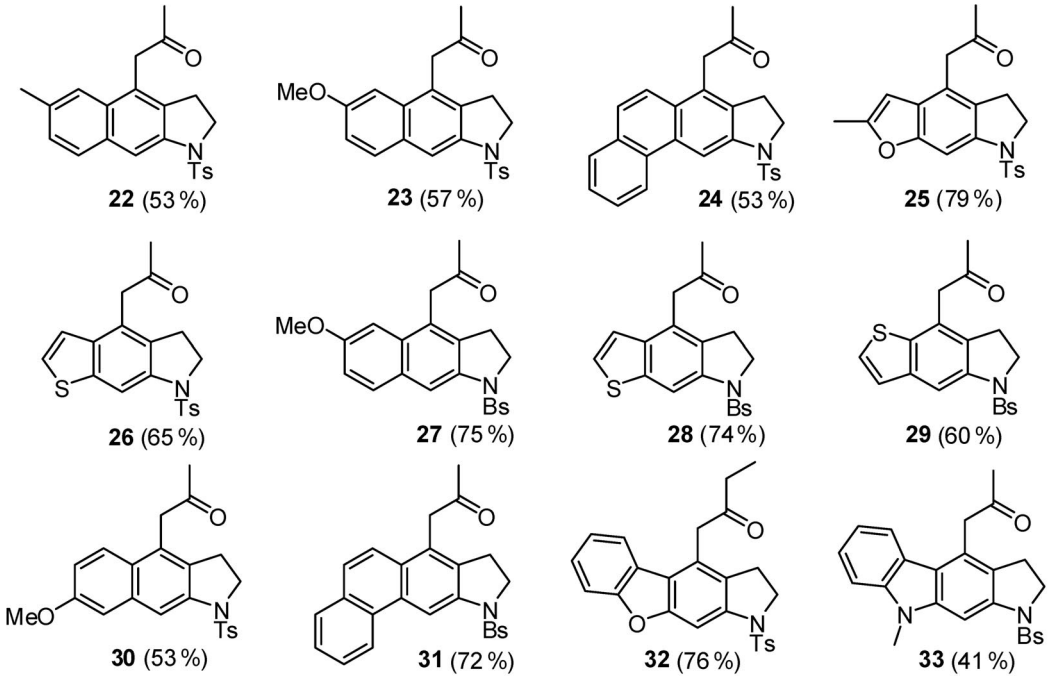


Fig. 4 A whole range of products was obtained by the successful cyclization of substrates with three atoms in the tether.

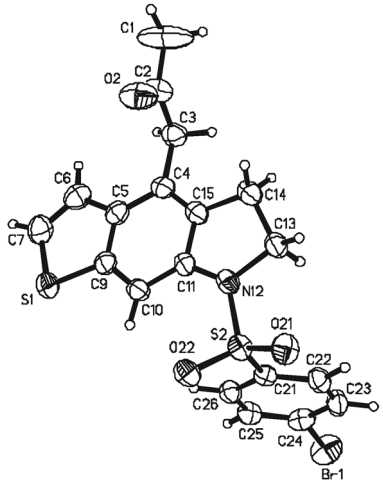
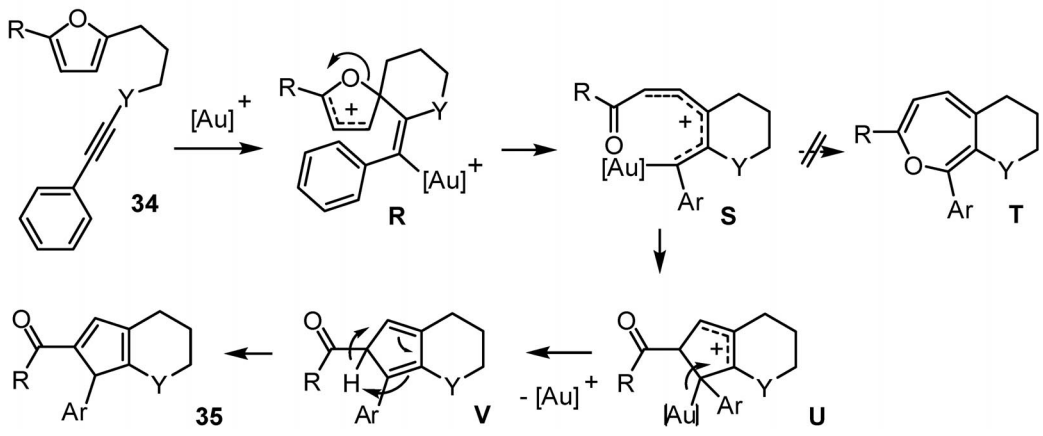


Fig. 5 ORTEP plot of the solid-state structure of the annelated thiophene **28**.

Most unexpectedly, the result was quite different with four atoms in the tether. Scheme 10 shows the reaction pathway taken now. After coordination of the triple bond of substrate **34**, a similar initial cyclization was induced, but due to the longer tether now a 6-*exo-dig* cyclization formed a six-membered ring in **R**. Computational chemistry shows that **R** occupies a different conformation than the five-membered intermediate **N**. Thus, a second ring closure could occur here, the system underwent a ring opening to **S**. **S** resembles the intermediate **C** from the gold-catalyzed phenol synthesis, but due to the additional aryl group donor, no nucleophilic attack of the carbonyl oxygen atom to deliver the oxepine **T** was observed. Instead, the pentadienyl cation substructure of **S** underwent an electrocyclic ring closure to **U**, eliminated the gold complex to **V** and formed the final product **35**.



Scheme 10 Annelated cyclopentadienes are formed with four atoms in the tether (Y = NR'; R = alkyl; Ar = aryl).

Different products obtained in the case of substrates with four atoms in the tether are shown in Fig. 6. Out of the different isomers of the cyclopentadiene substructure which are conceivable and potentially interconvert by 1,5-H shifts, the one depicted seems to be the most stable one. This is not only supported by the spectroscopic data of **36–38**, but also by the crystal structure analysis of product **37** as shown in Fig. 7. The hydrogen atom at the five-membered ring is clearly at the position labeled C-3, the tolyl substituent at that ring is at the tetrahedral carbon, the other four carbon atoms being planar and show bond lengths of a normal localized 1,3-diene substructure.

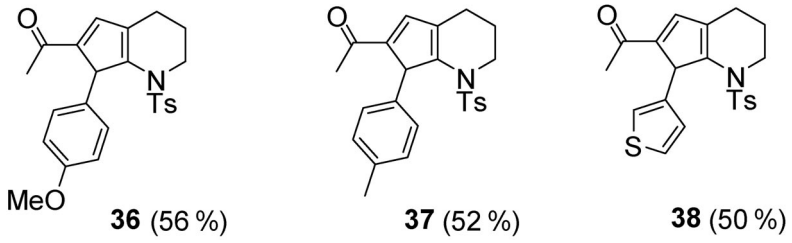


Fig. 6 Acylcyclopentadienes obtained by gold-catalyzed conversion of substrates with four atoms in the tether.

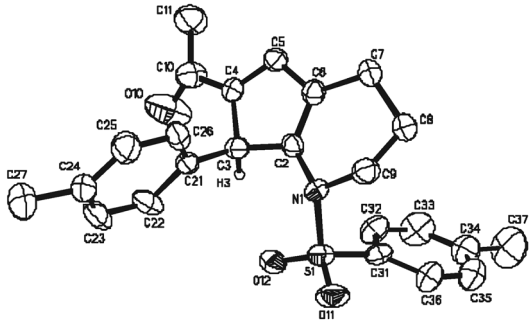


Fig. 7 ORTEP plot of the solid-state structure of the annelated tolylcyclopentadiene **37**.

ARE THERE MORE SWITCHES OF THE REACTION PATHWAY WITH FURANYNE SUBSTRATES POSSIBLE?

These interesting and very useful variations of the reaction pathway of the furanyne cyclization show the synthetic potential of this class of substrates. Especially in the field of the synthesis of heterocycles (for the huge benefits of gold catalysis for organic synthesis, see, e.g., [45–47]), there is still an enormous potential, and the future will show what other conversion will be possible. Apart from the mechanistic aspects, the synthetic benefit will strongly depend on a simple access to the substrates. Here the availability of some furan derivatives from renewable resources constitutes an additional benefit [48]. Furthermore, the recently developed possibility of isolating vinylgold species [49] and the option to do a palladium-catalyzed cross-coupling with such species [50,51] might even further extend the synthetic options.

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