Homogeneous Gold Catalysts and Alkynes: A Successful Liaison

A. Stephen K. Hashmi

Institut für Organische Chemie, Universität Stuttgart,
Pfaffenwaldring 55, D-70569 Stuttgart, Germany
http://www.hashmi.de

Abstract: The use of the combination of homogeneous gold-catalysts and alkynes in organic synthesis is reviewed from its beginnings in C-N-bond formation to the newest developments in C-C-bond formation. The common basic principle of these reactions is discussed. Special attention is devoted to the question where the gold catalysts are superior to either other catalysts or more traditional synthetic approaches to the product molecules.

Transition metal catalysis has become one of the most important tools in organic synthesis. It allowed entirely new transformations which were not possible previously by "traditional" organic reactions and thus significantly increased the efficiency of synthesis. It also made retrosynthetic analysis more demanding as many of the transformations go along with a remarkable increase in molecular complexity (1) which makes the relationship between the product and the starting material more difficult to recognize. In many of these reactions, especially in the case of late transition metals, C-C multiple bonds in either alkenes or alkynes, are the site of reaction.

Theoretical background

In the field of homogeneous gold catalysis the alkynes **1**, which have the structural motive of a C-C-triple bond, belong to the most popular substrates. The reason for that popularity is the high reactivity of the alkynes which originates from their electronic structure (2). Often the corresponding alkenes with their C-C-double bond are less reactive.

On one hand, the alkynes possess two orthogonal π-orbitals high in energy occupied by two electrons each. These react with electrophilic reagents (E) like halogens in organic synthesis or electrophilic metal centers like gold (in the oxidation states I or III) in the field of transition metal catalysis (3,4). In the interaction with a metal center both the π-orbital in the plane of metal co-ordination and the π-orbital perpendicular to it are able to interact with the d-orbitals of the metal.

On the other hand, the lowest unoccupied orbital of the alkynes is low in energy and thus eagerly react with *strong nucleophiles* like for example ethyne **2** with catalytical amounts of alkoholates in the Reppe synthesis of vinyl ethers **3** (5).
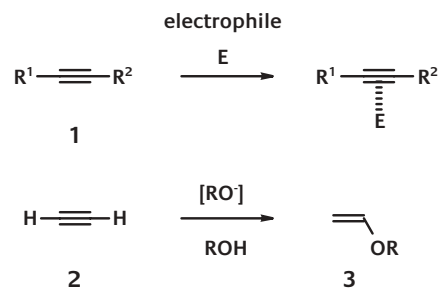

Most unfortunately, *weak nucleophiles* (Nu) do not react directly with the alkynes, although this is often desired in organic synthesis. But the alkyne can be activated by co-ordination to the electrophilic gold complexes as mentioned above. This co-ordination withdraws electron

density from the alkyne and thus makes the alkyne more electrophilic, now the desired attack of *weak nucleophiles* is possible, too.

Several examples for this π-mode of co-ordination to both gold(I) and gold(III) are known in the literature (6,7,8), some examples have even been characterized by X-ray crystal structure analyses (9,10). Here the C-C-bond length increases from 1.19 Å, a normal value for an alkyne, to 1.26 Å. This is exactly what one would expect when electron density is withdrawn from a bonding orbital of the alkyne by the electrophilic gold. Simultaneously the Au-C-bond length between 2.05 and 2.10 Å is quite short and thus reflects a very strong bond of that electrophile with the alkyne. Furthermore even a chelating π-co-ordination to bis-alkynes has been proven (11,12).

Only for terminal alkynes **4** and ethyne itself, which both bear a hydrogen atom at one end of the C-C-triple bond, a second mode of interaction, especially with gold(I)-complexes, is well known. The gold replaces this hydrogen atom in the presence of a base which takes up the hydrogen atom as a proton and forms gold(I)-alkynyl complexes **5**. The latter are stable, can be isolated and the alkynyl units do not readily react with nucleophiles (13).

Occasionally both structural motives, the π-co-ordination and a gold-alkynyl-σ-bond like in **6** can be found in some structures (14,15).
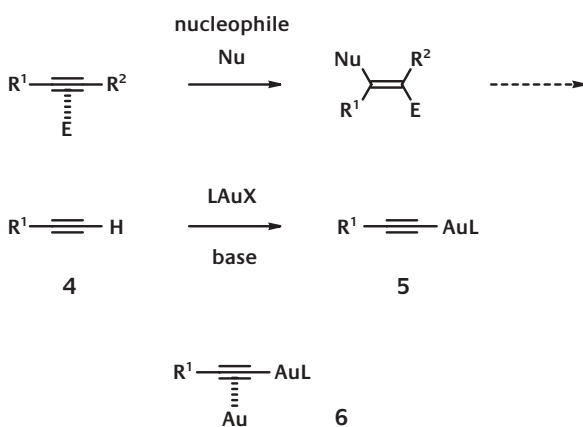
The beginning

Singular and scattered reports on the activation of C-C-triple bonds (16) demonstrated that gold(III) can be superior to mercury(II) in activating alkynes for the addition of nucleophiles like H_2O or Cl^-. At that time mercury(II) in acidic medium was considered to be *the* far most active catalyst for the addition of H_2O to alkynes (17). The first one to really recognize the advantages of gold catalysts by a logical approach was Hutchings in 1985 (18). He successfully applied this principle for the heterogeneous catalysis of the

hydrochlorination of ethyne **2** to vinyl chloride **7**, an important building block for vinyl polymers; this has been reviewed recently (19,20).
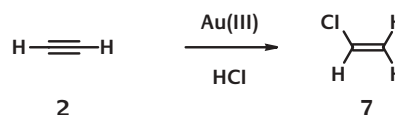
Reaction with Nitrogen-nucleophiles

In 1987 Utimoto *et al*. looked for an effective catalyst for the intramolecular nucleophilic addition of the amino group in **8** to the alkyne, a cyclization to the six-membered heterocycle tetrahydropyridine **10**. The two steps involved are the addition of the amine to the alkyne followed by the tautomerization of the intermediate enamin **9** to the imin in the product **10**. At that time palladium(II) and mercury(II) were *the* species known to activate C-C-multiple bonds for the addition of nucleophiles, but they gave poor results with the substrates of type **8**. Utimotos group discovered that while 5 mol% of palladium(II)-complexes at 97°C gave a 70% yield after 20 hours, 5 mol% of $Na[AuCl_4] \cdot H_2O$ delivered a *quantitative yield* after *only 12 hours at room temperature* (21,22).
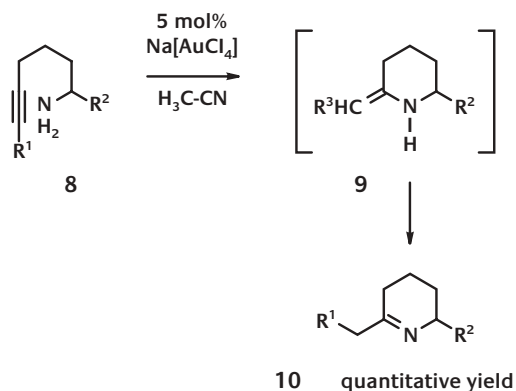
The corresponding 4-alkynylamines **11** and 3-alkynylamines **12** selectively cyclized to the related dihydropyrrols **15**. In **11** the nucleophile can still reach the internal end of the C-C-triple bond and form the enamin **13**, in **12** only the outer carbon atom of the alkyne can be attacked and the enamin **14** is the intermediate. Both types of heterocycles are frequently found in natural products, and Utimoto also used this methodology for the synthesis of some natural products. Gold complexes still range among the most effective catalysts for the intramolecular amination of triple bonds (23), especially because unlike with the newer lanthanoide catalysts (where one often has to work in a glove-box!)(24,25), it is not necessary to thoroughly exclude humidity and oxygen, the gold-catalysts are quite robust.

11 → **13**

13 → **15** > 98% yield

12 → **14**

5 mol% Na[AuCl$_4$], H$_3$C-CN
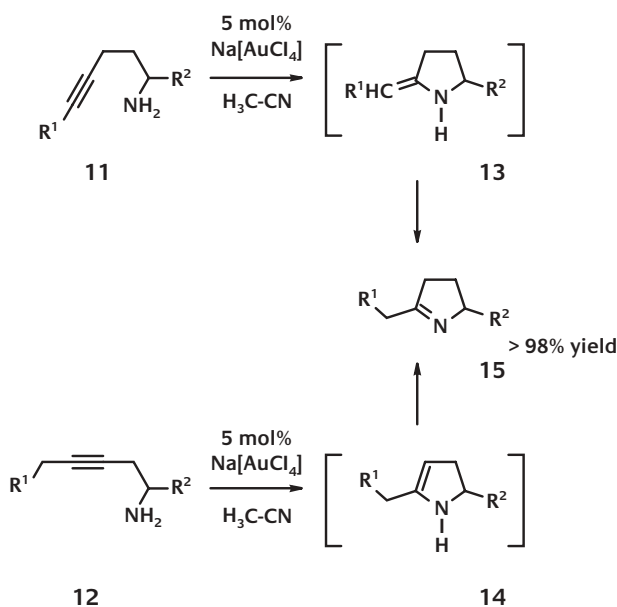
In 1996 Lok *et al.* used the cationic [Au(S(CH$_2$)$_5$)]$^+$BF$_4^-$ for intramolecular cyclizations to dihydropyrimidene-heterocycles **16** (26). Here the rate of reaction is the same as in the catalysis by AgBF$_4$.
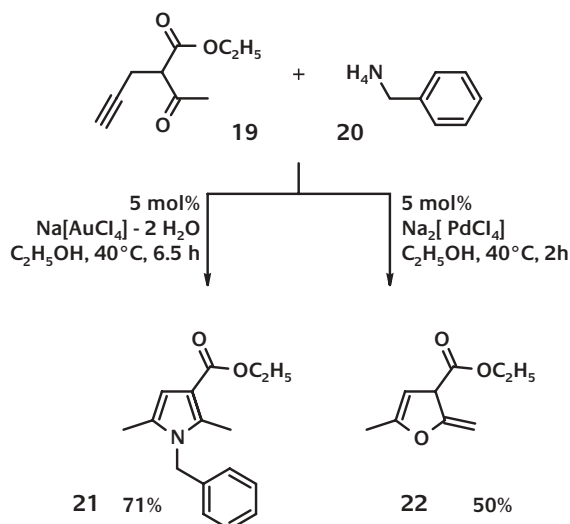

16 (no yield given)
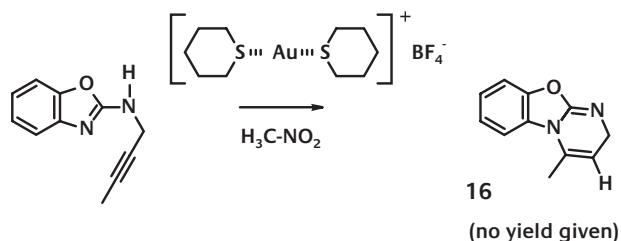
T. E. Müller *et al.* investigated serveral different transition metal complexes and he found that a gold(III)-phosphine complex with weakly co-ordinating nitrate counter ion was the most active gold complex, albeit for his test substrate a cationic copper(I)-catalyst possessed the highest activity (27,28). While he first was unable to repeat Utimotos results (27), he later obtained a quantitative yield with a modified catalyst, too (28).

17 → **18** 75%

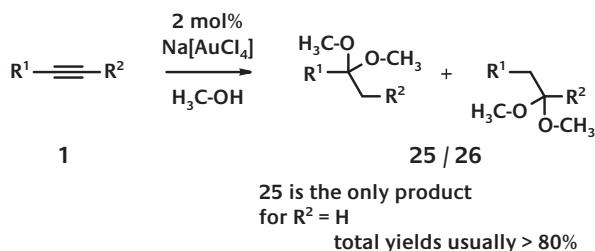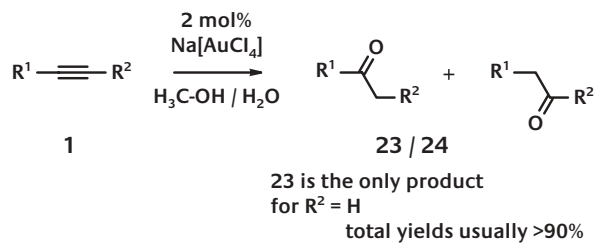5 mol% Na[AuCl$_4$] - 2 H$_2$O, C$_2$H$_5$OH, 60°C, 2 h
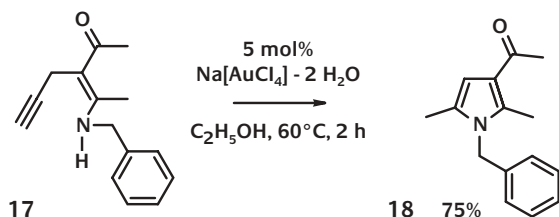
Quite recently Arcadi *et al.* reported that the aromatic heterocycle pyrrole **18** can be formed from the enynes **17**. Even the condensation of primary amines with ketones is accelerated by Na[AuCl$_4$] · 2 H$_2$O (29). Thus both steps, the attachment of the nucleophilic amino-group of **20** and the intramolecular cyclization with the alkyne of **19** can be

conducted in an efficient one-pot procedure delivering **21**. The related palladium catalyst only leads to the furan-derivative **22**, no condensation of the carbonyl group with the amine was observed.

19 + **20**

5 mol% Na[AuCl$_4$] - 2 H$_2$O, C$_2$H$_5$OH, 40°C, 6.5 h

5 mol% Na$_2$[PdCl$_4$], C$_2$H$_5$OH, 40°C, 2h

21 71%

22 50%

Reaction with oxygen-nucleophiles

Utimoto *et al.* immediately recognized that other, weaker nucleophiles should also add to alkynes in the presence of gold-catalysts. They therefore investigated the addition of water to the alkynes **1** (30). Synthetically, this is an interesting and attractive equivalent of the Wacker oxidation of olefins to produce ketones (31), because it lacks the necessity of an *in-situ* reoxidation of the catalyst. With 2 mol% of Na[AuCl$_4$] in a methanol/water mixture after one hour the ketone was obtained, with pure methanol dimethylketals were isolated. Internal alkynes (R and R^2 ≠ H) reacted slowly and delivered mixtures of the two conceivable isomers **23/24** or **25/26**.

1 → **23 / 24**

2 mol% Na[AuCl$_4$], H$_3$C-OH / H$_2$O

23 is the only product for R^2 = H
total yields usually >90%

1 → **25 / 26**

2 mol% Na[AuCl$_4$], H$_3$C-OH

25 is the only product for R^2 = H
total yields usually > 80%

Substrates with an alkohol group next to the alkyne reacted sluggishly, protection with an ester or an ether group removed that problem. Furthermore these protection groups solved the problem of selectivity. The ether **27** directed the nucleophile to the remote carbon atom and after the ketone **28** is formed, the alcohol is eliminated to deliver an unsaturated ketone **29** (32), while the ester **30** directed the nucleophile to the adjacent carbon atom of the triple bond (to **31**). For organic synthesis the formation of **29** is a non-acidic equivalent of the Meyer-Schuster rearrangement (33) of propargylic alcohols.
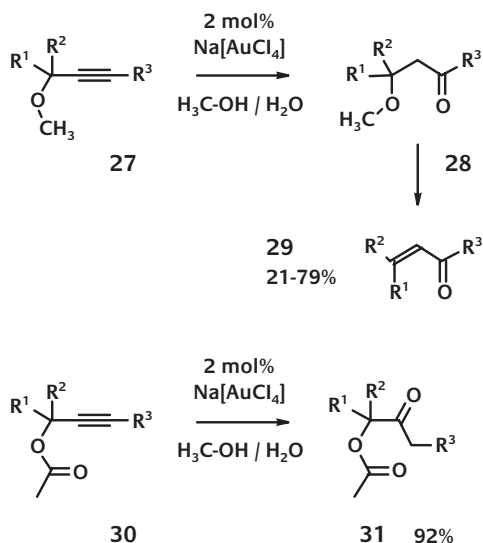
In 1992 a Japanese patent took up this idea, they reported the synthesis of acetals from alkynes and alcohols by different gold catalysts (34).

Utimoto *et al.* also claimed that gold(I)-complexes were ineffective for these conversions, but they only tried $K[Au(CN)_2]$, a co-ordinatively saturated gold(I)-complex with two strong cyanide ligands which are barely substituted by the alkyne in the substrate. Lok *et al.* were the first to apply a cationic gold(I) catalyst, but the latter was still co-ordinatively saturated with two strong ligands. They also stated that neither $K[Au(CN)_2]$ nor $Au(PPh_3)Cl$ were active (26). In 1998 Teles *et al.* at BASF AG reinvestigated the addition of water and alcohols to the alkynes and discovered that a co-ordinatively unsaturated, cationic gold(I)-species $[LAu]^+$ was a highly effective catalyst. Turnover numbers of up to 10^5 and turnover frequencies of up to 5400 h^{-1} could be reached (35,36).

One other remarkable finding of Teles' stems from calculations of the reaction pathway. These suggest that, different from the usual attack of the nucleophile (Nu) from the side opposite to the co-ordinated metal (**32** → **33**) as assumed for other electrophilic metals (Met)(37), gold(I) directs the alcohol nucleophile to the side of the coordinated metal (**34 6 35**).
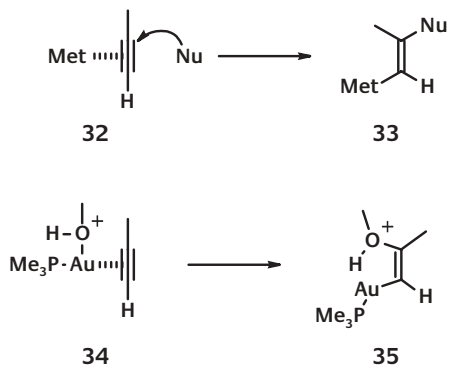

Just recently Tanaka *et al.* used similar reagents for the generation of the catalytically active gold(I) species to catalyze the addition of water to alkynes. They reported that in aqueous methanol a solvent with as little as 0.005 mol% catalyst excellent yields of the desired ketones could be obtained and turnover frequencies of up to 14000 h^{-1}, with 1 atmosphere of carbon monoxide as additive even 15600 h^{-1}, were reached (38).

C-C-bond formation

The first example of a C-C-bond formation was reported by Gasparrini *et al.* (39). It is quite difficult to recognize how two of the alkynes **36** and some nitrogen and oxygen containing molecules, most probably nitrile oxides, are assembled to the oxazoles **37**.
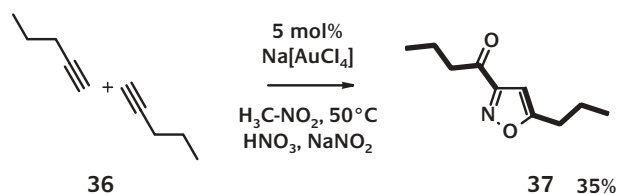
In 2000 my research group discovered the gold catalyzed isomerization of furans **38** which possess alkynyl groups to the corresponding highly substituted and anellated arenes **39** (40). Alkyl, aryl (41) and alkynyl substituents are tolerated.

Y = CR$_2$, O, NR
R^1 = alkyl, aryl, alkynyl
R^1, R^2, R^3 = alkyl
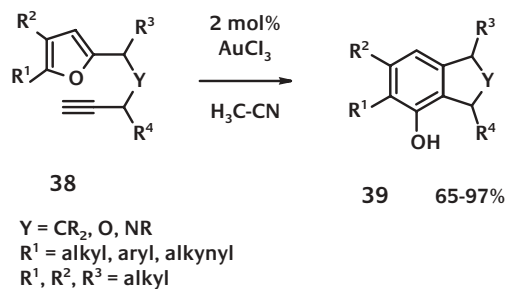
In this catalysis reaction gold(III) was clearly the most active catalyst (42), in fact with other transition metal-

catalysts the reaction is so slow that it probably would never have been detected (and thus discovered). The kinetic data for the different metals is compared in Figure **1**, please notice that gold was too active to measure the kinetics above +10°C while the other metals needed +50°C to give detectable rates.

The advantage of this route to arenes is the selectivity. It is not trivial to construct highly substituted arenes in a selective manner, often significant amounts of side-products are formed. Here this problem is shifted to a selective synthesis of a furan heterocycle, which is much easier. Some furans are even accessible from carbohydrates (43) and thus are renewable feedstocks (furfural for example is produced from agricultural waste). In this remarkable reaction four or even five new bonds (42) are formed.

Subsequently Dankwardt demonstrated that apart from the electron rich furan as a nucleophilic reaction partner, also silyl enol ethers like in **40** can be offered intramolecularly (44). In this case the products are functionalized naphthalenes **41**. While here the yields obtained with the gold-catalyst were low and inferior to the yield from some rhodium-catalysts, when the pyrrole in **42** was used as a nucleophile, the best yield was obtained with gold(III)-catalysts; now the alkyne attacks the 3-position of that heterocycle and yields the benzoindole **43**.


40 → **41** 37%

42 → **43** 97%
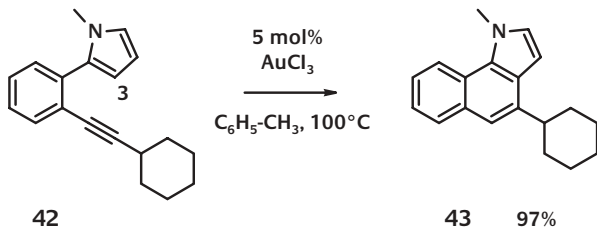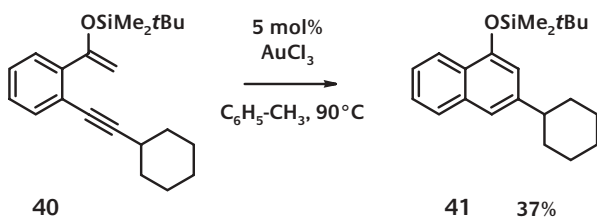
The latest finding was Yamamoto´s truely remarkable synthesis of naphthylketones from easily accessible *o*-alkynyl benzaldehydes **44** (45). Here once again the alkyne is activated for the intramolecular attack of a weak nucleophile, the oxygen atom of the carbonyl group, the intermediate then undergoes an intermolecular cycloaddition with the second alkyne **1**. Finally an 1,4-elimination leads to the product **45**.


45 52-96% yield
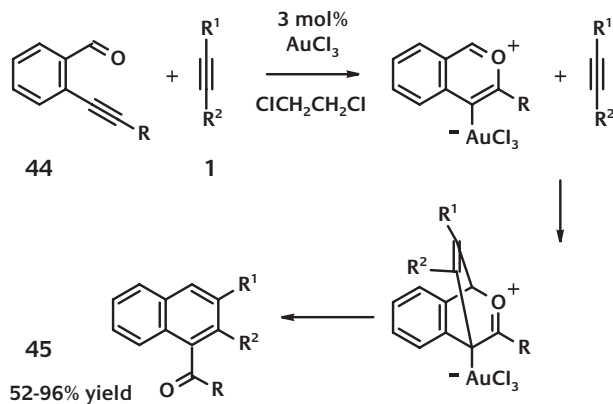
Reactions of the isomeric allenes

Allenes are isomers of the alkynes which possess a cumulated system of two C-C-double bonds instead of the C-C-triple bond, thus one would expect their chemistry to reflect the activation of C-C-multiple bonds by gold as well. Very helpful in this context is the additional strain that goes along with the sp-hybridized carbon atom in the center of the allene and which additionally activates the olefin. My group found that allenyl ketones **46** could efficiently be cycloisomerized with $AuCl_3$ in acetonitrile (46). Apart from the corresponding furans **48**, which were known to be formed in the Ag(I) catalyzed Marshall reaction (47) as well (but with up to 30 mol% of $AgNO_3$), with the gold catalyst an unexpected dimer 49 was formed. This dimer is a constitutional isomer of the dimer **47** from palladium(II) catalyzed reactions (48). Furthermore, and synthetically most relevant, a cross-dimerization of the allenyl ketones **46** and vinyl ketones **50** to **51**, which never worked with the palladium catalysts, was possible with the gold catalyst (46).
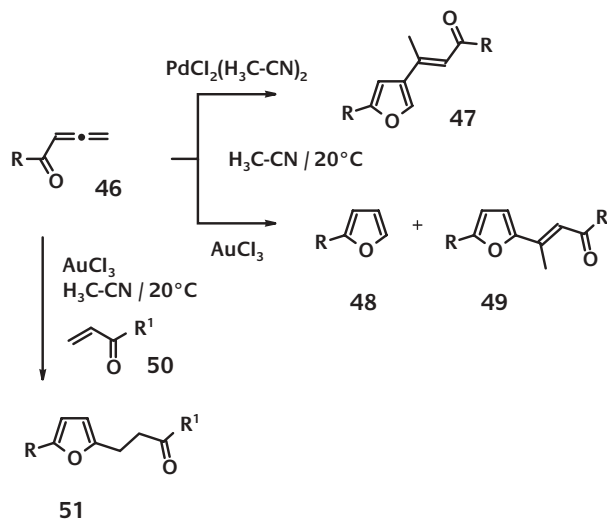
Krause *et al.* took up this principle for the cyclization of enantiomerically pure allenyl carbinols **52** to dihydrofurans

53 in a perfectly stereocontrolled manner (49). Especially with acid sensitive substrates gold was superior to other methods like the acidic Amberlyst 15 resin. Moreover, even compared to Marshall´s well-established Ag(I) catalyzed cyclization of allenyl carbinols (50,47,51), $AuCl_3$ increases the rate and thus allows the cyclization of notoriously different substrates like silyl ethers.

52   **53**
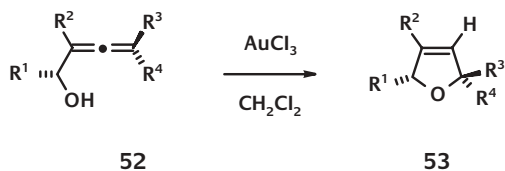
Conclusion

Gold catalysts have already proven their benefits in the homogeneous catalysis of organic reactions involving the C-C-triple bonds of alkynes as functional groups. Isomers of the alkynes, the allenes react in a similar manner. The common principle of all these reactions is the electrophilic activation of the C-C-multiple bond by a co-ordination to gold. Often the activity of the gold catalysts is higher than the activity of other known catalysts or they selectively form other products. Especially the new C-C-bond forming reactions will probably initiate more intensive efforts in the utilization of gold catalysts in organic reactions, covering both homogeneous catalysis and heterogeneous catalysis.

One open question is still the oxidation state of the catalyst. Hutchings found gold(III) to be most active. The crystal structure analyses also provide evidence for a strong back-donation in the d^{10}-gold(I) complexes. This means the electophilic activation should be diminished by such a back-donation. On the other hand, the gold catalyst with the highest activity known so far is Teles gold(I) catalyst. Still we should remember that what we put into the flask might be only a pre-catalyst; gold(III) might be reduced *in-situ* by the unsaturated organic substrate, gold(I) might disproportionate to gold(0) and gold(III). It becomes evident that there still remains a lot to be done to achieve a full understanding.

Acknowledgements

About the Author

A. Stephen K. Hashmi is professor for organic chemistry at the University at Stuttgart. He carried out his Diploma and PhD with Professor G. Szeimies at the Ludwigs-Maximilians-Universität München in the field of strained organic compounds. His postoc with Professor B. M. Trost at Stanford University covered transition metal catalysis. His time with Professor J. Mulzer at the Freie Universität Berlin, Johann Wolfgang Goethe-Universität Frankfurt and Univertsität Wien, as well as during visits at the University of Tasmania and the Universität Marburg focused on both stoichiometric organometallic chemistry and transition metal catalyzed organic reactions, which are still the major topics in the group.

References

1 S.H. Bertz, *J. Am. Chem. Soc.*, 1982, **104**, 5801

2 D.A. Plattner, Y. Li and K.N. Houk in *Modern Acetylene Chemistry* (Eds.: P.J. Stang and F. Diederich), VCH, Weinheim, 1995, pp 1

3 J.P. Collman, L.S. Hegedus, J.R. Norton and R.G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California, 1987, p 42 and p 156

4 G.G. Melikyan and K.M. Nicholas in *Modern Acetylene Chemistry* (Eds.: P.J. Stang and F. Diederich), VCH, Weinheim, 1995, p 99

5 V. Jäger and H.G. Viehe in *Houben-Weyl*, Thieme, Stuttgart, 1977, Vol. 5/2a, p 738

6 R. Hüttel and H. Forkl, *Chem. Ber.*, 1972, **105**, 1664

7 R. Hüttel and H. Forkl, *Chem. Ber.*, 1972, **105**, 2913

8 G. Wittig and S. Fischer, *Chem. Ber.*, 1972, **105**, 3542

9 R.M. Dávila, R.J. Staples, J.P. Fackler, Jr., *Organometallics*, 1994, **13**, 418

10 P. Schulte and U. Behrens, *Chem. Commun.*, 1998, 1633

11 K. Köhler, S.J. Silverio, I. Hyla-Kryspin, R. Gleiter, L. Zsolnai, A. Driess, G. Huttner and H. Lang, *Organometallics*, 1997, **16**, 4970

12 W. Frosch, S. Back, K. Köhler and H. Lang, *J. Organomet. Chem.*, 2000, **601**, 226

13 This has been reviewed: H. Schmidbaur, A. Grohmann and M.E. Olmos, Gold: Progress in Chemistry, Biochemistry and Technology (Ed. H. Schmidbaur), Wiley, 1999, p 647 (more specific pp 654-661)

14 G.E. Coates, G. Parkin, *J. Chem. Soc.*, 1962, 3220

15 D.M.P Mingos, J. Yan, S. Menor and D.J. Williams, *Angew. Chem.*, 1995, **107**, 2045; *Angew. Chem. Int. Ed.*, 1995, **34**, 1894

16 R.O.C. Norman, W.J.E. Parr and C.B. Thomas, *J. Chem. Soc., Perkin Trans. I*, 1976, 1983

17 V. Jäger and H.G. Viehe in *Houben-Weyl*, Thieme, Stuttgart, 1977, Vol. 5/2a, p 726

18 G.J. Hutchings, *J. Catal.*, 1985, **96**, 292

19 G J. Hutchings, *Gold Bull.*, 1996, **29**, 123

20 G.J. Hutchings, *Catal. Today*, 2002, **72**, 11

21 Y. Fukuda, K. Utimoto and H. Nozaki, *Heterocycles*, 1987, **25**, 297

22 Y. Fukuda and K. Utimoto, *Synthesis*, 1991, 975

23 T.E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675, specifically p 684

24 G.A. Molander, E.D. Dowdy, S.K. Pack, *J. Org. Chem.*, 2001, **66**, 4344

25 S. Hong, T.J. Marks, *J. Am. Chem. Soc.*, 2002, **124**, 7886 (experimental details in the supporting information)

26 R. Lok, R.E. Leone and A.J. Williams, *J. Org. Chem.*, 1996, **61**, 3289

27 T.E. Müller, *Tetrahedron Lett.*, 1998, **39**, 5961

28 T.E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter and Y.-K. Yan, *Organometallics*, 2000, **19**, 170

29 A. Arcadi, S. Di Giuseppe, F. Marinelli and E. Rossi, *Adv. Synth. Catal.*, 2001, **343**, 443

30 Y. Fukuda and K. Utimoto, *J. Org. Chem.*, 1991, **56**, 3729

31 J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier and J. Sabel, *Angew. Chem.*, 1962, **74**, 93; *Angew. Chem. Int Ed.*, 1962, **1**, 80

32 Y. Fukuda and K. Utimoto, *Bull. Chem.* Soc. *Jpn.*, 1991, **64**, 2013

33 K. Meyer and K. Schuster, *Chem. Ber.*, 1922, **55**, 819

34 Y. Fukuda and K. Uchimoto, JP 04103552, 1992 [*Chem. Abstr.*, 1992, **117**, 150554]

35 J.H. Teles and M. Schulz (BASF AG), WO-AI 9721648, 1997 [*Chem. Abstr.*, 1997, **127**, 121499]

36 J.H. Teles, S. Brode and M. Chabanas, *Angew. Chem.*, 1998, **110**, 1475; *Angew. Chem. Int. Ed.*, 1998, **37**, 1415

37 J.P. Collman, L.S. Hegedus, J.R. Norton and R.G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California, 1987, p 416

38 E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem.*, 2002, **114**, 4745; *Angew. Chem. Int. Ed.*, 2002, **41**, 4563

39 F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile, G. Palmieri and L. Maresca, *J. Am. Chem. Soc.*, 1993, **115**, 4401

40 A.S.K. Hashmi, T.M. Frost and J.W. Bats, *J. Am. Chem. Soc.*, 2000, **122**, 11553

41 A.S.K. Hashmi, T.M. Frost and J.W. Bats, *Catal. Today*, 2002, **72**, 19

42 A.S.K. Hashmi, T.M. Frost and J.W. Bats, *Org. Lett.*, 2001, **3**, 3769

43 F.W. Lichtenthaler, *Acc. Chem. Res.* 2002, **35**, 728

44 J.W. Dankwardt, *Tetrahedron Lett.*, 2001, **42**, 5809

45 N. Asao, K. Takahashi, S. Lee, T. Kasahara and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 12650

46 A.S.K. Hashmi, L. Schwarz, J.-H. Choi and T.M. Frost, *Angew. Chem.*, 2000, **112**, 2382; *Angew. Chem. Int. Ed. Engl.*, 2000, **39**, 2285

47 J.A. Marshall and K.G. Pinney, *J. Org. Chem.*, 1993, **58**, 7180

48 A.S.K. Hashmi, T.L. Ruppert, T. Knöfel and J.W. Bats, *J. Org. Chem.*, 1997, **62**, 7295

49 A. Hoffmann-Röder and N. Krause, *Org. Lett.*, 2001, **3**, 2537

50 J.A. Marshall and X.-j. Wang, *J. Org. Chem.*, 1991, **56**, 4913

51 J.A. Marshall and G.S. Bartley, *J. Org. Chem.*, 1994, **59**, 7169