CHEMICAL REVIEWS

Review

Alternative Synthetic Methods through New Developments in Catalysis by Gold

Antonio Arcadi

Chem. Rev., **2008**, 108 (8), 3266-3325 • DOI: 10.1021/cr068435d • Publication Date (Web): 24 July 2008

Chemical Reviews is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Alternative Synthetic Methods through New Developments in Catalysis by Gold

Antonio Arcadi*

Department of Chemistry, Chemical Engineering and Materials, University of L'Aquila, via Vetoio, 67010 Coppito (AQ), Italy

Received January 14, 2008

Contents

1. Introduction

Synthetic chemists are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules.[1] Recently, there has been an impressive focus on the pursuit of organic chemists to design and successfully apply the ideal synthesis in terms of efficiency, with atom and step economy being a major goal.[2] Some of the challenges for chemists have included the discovery and development of new synthetic pathways using alternative reaction conditions and solvents for improved selectivity and energy minimization and the design of less toxic and inherently safer chemicals. Significant progress has been made in the improvement of sustainability[3] and the role of catalysis as a key technology to achieve the objectives of sustainable chemistry has been considered.[4] The area of catalysis is sometimes referred to as a "foundational pillar" of green chemistry.[5] Catalytic reactions often reduce energy requirements and decrease separations because of increased selectivity; they may permit the use of renewable feedstocks of less toxic reagents or minimize the quantities of reagents needed. New catalytic organic synthesis methodologies thus have offered several possibilities for a relevant improvement in the eco-compatibly of fine chemical production, allowing a drastic decrease in the *E* factor. [The *E* factor is defined as the ratio (by weight) of byproduct to the desired product formed.] Many research activities in this field have been based on the realization of new green catalytic systems that provide resource-saving synthetic methodologies through transition metal-catalyzed reactions.[6] Recently, the discovery that gold can be prepared in catalytically active forms has spurred growing interest in investigation of the chemical and catalytic properties of gold.[7] Gold catalysts, because of their unique properties, have now become a well-established best choice for many chemical transformations with pre-eminence established now in both heterogeneous and homogeneous processes. Indeed, gold catalysts can carry out processes for which no other catalyst has yet been identified, and the exploitation of gold catalysts for commercial applications is being pursued.[8] It is also at the heart of a number of new developments in green technology,[9] and its ambient temperature activity, in particular, has opened up new opportunities for pollution control applications.[10] The principles of green chemistry include prevention of waste, use of renewable feedstocks, use of catalysts rather than stoichiometric reagents, use of safer solvents and reaction conditions, and increased energy efficiency: catalysis by gold could help in all these areas. Moreover, from an environmental point of view, gold catalysts show many valuable features. Metallic gold is biocompatible and has anticancer activity; gold(III) compounds have been reported to be appreciably stable under physiological-like conditions and to manifest relevant anti-

* To whom correspondence should be addressed. E-mail: arcadi@univaq.it.

10.1021/cr068435d CCC: $71.00

Antonio Arcadi was born in Stignano, Italy, in 1954. He obtained his laurea degree in Medicinal Chemistry and Technology at the University "La Sapienza" of Rome in 1978 under the guidance of Pr. S. Cacchi. In 1979, he joined the Institute of Chemistry at the University of L'Aquila to undertake a teaching fellowship and research activities on organometallic chemistry directed towards organic synthesis. He was appointed Associate Professor of Organic Chemistry in 1992 at the University of Urbino and then (2002) to the Chair of Organic Chemistry of the University of L' Aquila. His current research interests lie in the area of developing new synthetic methodologies through transition-metal catalysis. Considerable efforts are concentrated on the reactions of alkynes bearing a nucleophile close to the carbon−carbon triple bond with organo-palladium complexes. More recently, he is focusing in the development of gold catalysis in organic synthesis. Other achievements have been obtained in the field of domino reactions as useful tools of ″Green Chemistry″.

proliferative properties against selected human tumor cell lines.[11] Gold salts can promote chemical transformations at room temperature with reaction times of just minutes. This contrasts with other metal-catalyzed reactions that require higher temperatures and reaction times of hours or even days.[12] Furthermore the high reactivity of many metal complexes render the reactions they catalyze sensitive to both air and moisture and limits their practical utility. Conversely, gold derivatives are robust transition metal catalysts and their catalytic reactions adhere to the criteria of a straightforward experimental setup, air and moisture tolerance, and generation of only environmentally benign byproduct.[13] Beyond this practical benefit, the apparent redox stability of Au(I) complexes under ambient conditions allows the development of new modes of reactivity by precluding the traditional oxidative addition/reductive elimination cycles so prevalent in late transition-metal catalysis. In many transformations, gold catalysts do not need any other ligand to exert their catalytic activity. Gold-catalyzed reactions often proceed under mild conditions, and gold catalysts are active in extremely small amounts. Solvents play a critical role in "greening" synthetic chemistry. Gold catalysts can be used with alternative solvents which enable easy catalyst separation and recycle. Gold is more abundant than platinum, palladium, rhodium, and other metals that are used even in large scale processes. Recycling of gold used in stoichiometric technical application, in addition to the production in mines every year, determines a high stability of its price, which is advantageous from economic point of view for industrial applications. So far, a number of reviews focusing on gold catalysis in organic synthesis have appeared.[14] In particular, the wide scope of the homogeneous gold-catalyzed reactions of enynes to give access to complex or otherwise inaccessible products has been previously pointed out.[14i–k] The theoretical chemistry of Au has also been reviewed.[15] The impact of catalysis by gold toward sustainable chemistry have been highilighted by Ishida and Haruta.[16] This Review will cover a personal selection of alternative gold-catalyzed synthetic methods published until November 2007 in both homogeneous and heterogeneous catalysis. The Review is organized by chemical transformation, so both homogeneous and heterogeneous examples for the same reaction will be discussed in the same section. The gold-catalyzed cycloisomerization of enynes will be here only marginally described.

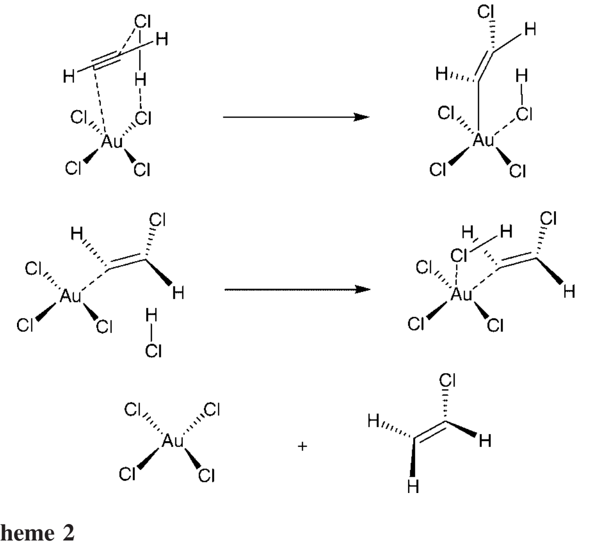
2. Gold-Catalyzed Additions to C−C Multiple Bonds

It is common knowledge that addition reactions to alkynes or olefins catalyzed by a Brønsted acid usually require harsh conditions and are plagued by numerous side reactions of the carbocation intermediate formed.[17] Replacement of the proton by Hg^{2+} constitutes a classical solution to this problem.[18] The "soft" character of this large and polarizable cation ensures a much greater affinity to the substrate, which ultimately translates into mild reaction conditions and high yields of the desired addition products. Spectroscopic data provide clear evidence that the ligand in the incipient π-complex is electron deficient and hence susceptible to attack by the nucleophile in the usual trans manner.[19] Although many addition reactions to alkynes occur with catalytic quantities[18,20] of Hg^{2+}, the resulting $C(sp^3)-Hg$ bond in the analogous reactions of alkenes is usually kinetically stable and requires an extra step to release the organic ligand. Thus, the overall transformation is rendered stoichiometric in toxic mercury salts. Such problems can be conveniently solved in many cases by the use of catalysis by gold.

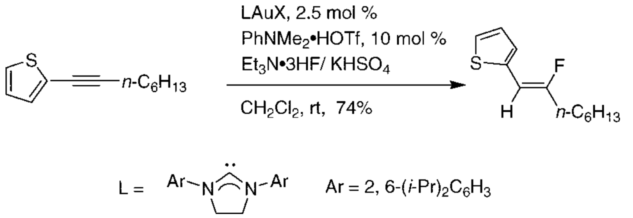
2.1. Hydrohalogenation of Alkynes

Hydrochlorination of acetylene is one method by which vinyl chloride can be manufactured on a commercial scale. Industrial processes use mercuric chloride supported on carbon,[21] but these catalysts can be short-lived because of their instability, with loss of mercuric chloride being a major catalyst deactivation mechanism, leading to environmental problems. In 1985, it was proposed that supported Au^{3+} would be a viable catalyst for alkyne hydrochlorination,[22] and later this was shown to be the case.[23] More recently, a detailed study of the hydrochlorination of acetylene and higher alkynes using a supported gold catalyst has been described.[24] A series of reactions using sequential exposure of the catalysts to C_2H_2 and HCl demonstrate that exposure to HCl before reaction of C_2H_2/HCl leads to enhanced activity, whereas exposure to C_2H_2 leads to deactivation. The key piece of mechanistic information is that which HCl adds in accordance with the Markovnikov rule and in an anti-manner to the alkyne. This anti-addition also has been observed in the hydrochlorination of acetylene using mechanically activated K_2PtCl_6,[25] for which it is proposed that the reaction could occur via a complex formed by adsorption of acetylene at a defect site on the surface of the mechanically activated K_2PtCl_6 and HCl adsorbed via hydrogen bonding with the surface Cl. It is feasible that a similar mechanism could operate with supported gold catalysts via the mechanism shown in Scheme 1, with gold tetrachloroaurate as the active species. The hypothesis is that the C_2H_2/Au/HCl complex is consistent with the high selectivity; the regeneration effect of HCl and the deleterious effect of C_2H_2 can explain polymerization, which is one of the mechanisms by

Scheme 1. Proposed Mechanism for the Hydrochlorination of Acetylene over Au/C



Scheme 2



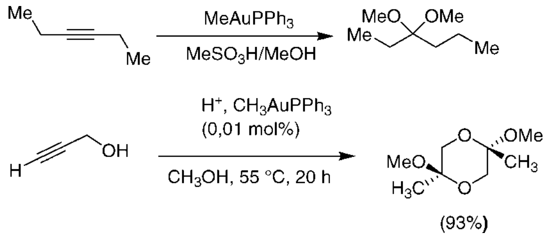
which catalyst deactivation occurs. DFT calculations indicate that the simultaneous coordination of alkyne and HCl to the Au(III) center of $AuCl_3$ is unlikely. The calculated transition state for HCl addition to the π-complex of C_2H_2 with $AuCl_3$ demonstrates that the stereochemistry of Cl addition is controlled by a hydrogen bond between HCl and a Cl ligand of Au. The anti-addition of HCl observed experimentally is then a consequence of a sequential addition of Cl and H to the alkyne.

The reactivity of higher terminal alkynes decreased with their steric bulk, and the internal alkynes were unreactive. Conversely, electrophilic (NHC)gold(I) complexes catalyze the *trans*-hydrofluorination of internal alkynes at room temperature, using a mild HF source (scheme 2). The procedure represents a new, selective, and potentially more versatile method for the synthesis of fluoroalkenes.[26] The substrate scope of this method includes dialkyl-, diaryl-, and aryl/alkyl- or thienyl/alkyl-substituted alkynes. Generally, fluoroalkenes are obtained indirectly,[27] and control over the stereochemistry often requires careful strategy.[28] For substrates bearing both a phenyl and an alkyl substituent, the predominance of β-fluorostyrene products is observed. Catalytic regioselectivities are higher for an electron-poor aryl substituent than for an electron-rich one; however, the electron-rich thienyl substituent also gave exclusive β-fluorination. No *gem*-difluoroalkanes are detected, and *trans*-hydrofluorination is observed in all cases.

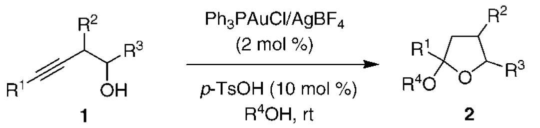
2.2. Hydration and Hydroxylation Reactions of Alkynes

The addition of water to alkynes is a synthetic method for generation of carbonyl compounds. Unlike many other syntheses of carbonyl compounds, the hydration of alkynes is an atom-economical addition without energy-intensive redox chemistry. Since Kucherov's observation in 1881 that mercury(II) salts catalyze the hydration of alkynes under mild conditions, the reaction has seen many applications in synthesis. The toxicity of mercury compounds and the problems associated with their handling and disposal make the Kucherov reaction unsuitable for modern, sustainable organic synthesis or any large-scale application. A steady development of alternative alkyne hydration catalysts has taken place, nurtured by the desire to replace mercury(II) by less-toxic and more-active metal catalysts.[29] The catalytic hydration of alkynes with a gold catalyst ($HAuCl_4$) was observed in 1976.[30] Later, a synthetically useful protocol appeared for alkyne hydration with sodium tetrachloroaurate ($NaAuCl_4$) as catalyst under almost neutral conditions. Terminal and internal alkynes are hydrated in excellent yields.[31] A variety of gold(III) organometallic compounds, containing Au$-C_6F_5$ or Au$-$Mes (Mes = 2,4,6-trimethylphenyl) units, and chloro ligands are precursors for the hydration of phenylacetylene and hept-1-yne under neutral or acidic conditions.[32] The best results were obtained with mononuclear complexes bearing electronegative ligands such as $NBu_4[Au(C_6F_5)_2Cl_2]$ or $PR_4[Au(ArI)Cl_3]$, whose activity was similar to that of $NaAuCl_4$. Higher turnover numbers were achieved in acidic media. Teles and co-workers claimed in a patent application that hydration of propargyl alcohol is catalyzed by an Au(I)-acid catalytic system.[33] Moreover, they reported the gold(I)-acid catalyzed addition of alcohols to alkynes.[34] The catalysts were generated from (a) $[AuX(PPh_3)]$(X = Cl, CF_3CO_2, $MeSO_3$, NO_3) and boron trifluoride, from (b) $[AuCl(PPh_3)]$ and AgY (Y = non-nucleophilic counterion), or from (c) $[AuMe(PPh_3)]$ by protonolysis of the gold$-$carbon bond with a strong acid that provides a non-nucleophilic counterion (H_2SO_4, HBF_4, $MeSO_3H$).[35] Reactions take place under mild conditions (20$-$50 °C) with a TOF of up to 5400 h^{-1}. The enol ethers formed can be hydrolyzed to form carbonyl compounds or trapped as ketals (Scheme 3).

Scheme 3



Scheme 4

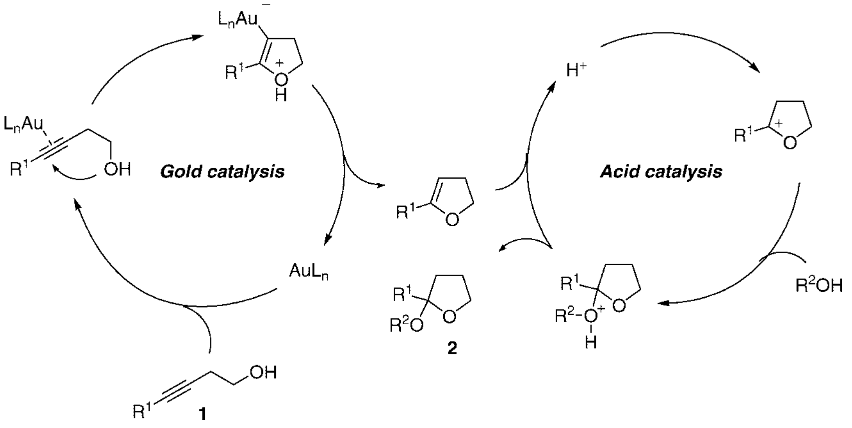


An intramolecular versions of this reaction has been reported in 2006 by Krause (Scheme 4).[36]

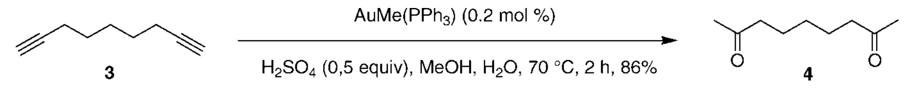
The strategy consists of a mild tandem cycloisomerization$-$hydroalkoxylation of homopropargylic alcohols **1** to tetrahydrofuranyl ethers **2**. The authors suggested that this two-steps transformation is probably catalyzed by a dual catalyst system consisting of a gold precatalyst and a Brønsted acid (Scheme 5).

Au(I)$-$acid systems in aqueous methanol were reported as powerful catalysts that promote the hydration of alkynes and have turnover frequencies of at least 2 orders of magnitude higher than the most efficient catalyst [*cis*-

Scheme 5



Scheme 6

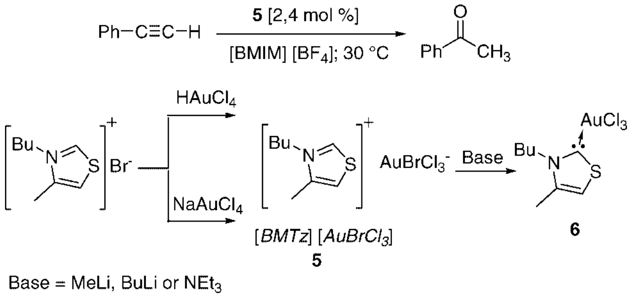


$PtCl_2(tppts)_2$] previously reported (tppts = $P(m\text{-}C_6H_4SO_3Na)_3$. The reaction did not proceed in the absence of either the Au catalyst or sulfuric acid.[37] The efficiency of the catalyst was significantly enhanced by addition of appropriate ligands [CO, $(PhO)_3P$], which enabled the quantity of the precious catalyst used to be minimized. Although the provenance of the ligand effect is ambiguous, it is envisaged to be associated with the stability of the catalyst. Other acid catalysts, such as CF_3SO_3H, CH_3SO_3H, and $H_3PW_{12}O_{40}$, also gave extremely high yields even in the absence of the coordinative additives. Terminal alkynes, both aliphatic and aromatic, were all able to undergo hydration under similar reaction conditions. Internal alkynes displayed a low reactivity, presumably because of steric hindrance. Propargyl alcohols also reacted smoothly, but they afforded mixtures of methyl ketones (Markovnikov addition) and α,β-unsaturated aldehydes (Meyer−Schuster reaction). A practical laboratory procedure for the hydration of 1,8-nonadiyne **3** to give 2,8-nonanedione **4** (Scheme 6), a useful synthetic intermediate for the synthesis of rootworm sex pheromones, has been published.[38] By contrast with the previous reported multistep procedures[39] resulting in massive waste of salts, the one-pot CH_3AuPPh_3-acid catalyzed hydration of 1,8-nonadiyne affords 1,8-nonanedione in 86% yield with a turnover frequency in methanol of 15 600 h^{-1}.

The complexes $[Au(PPh_3)(RCO_2)]$ or $[Au(PPh_3)(RSO_3)]$ have been proposed as catalyst precursors for hydration of terminal and internal alkynes in combination with boron trifluoride−diethyl etherate.[40] Of these, $[(Ph_3P)Au(C_2F_5CO_2)]$ was the most active compound investigated (TOF up to 3900 h^{-1} for hydration of hex-3-yne in MeOH at 70 °C), and it is even reusable. Cationic complexes of gold(I) incorporating heterocyclic imidazolylidene carbene ligands hydrate hex-3-yne,[41] and the catalytic hydration of phenylacetylene by a porphyrin complex [Au(TPP)Cl] (TPP = tetraphenylporphine) was noted.[42]

Catalytic hydration of phenylacetylene has been accomplished in ionic liquids using 3-butyl-4-methylthiazolium trichlorobromoaurate $[BMTz][AuCl_3Br]$ **5** as catalyst (Scheme 7).[43] The potential reuse of catalysts is an advantage achieved by recycling the ionic liquid phase. Various imidazolium-derived ionic liquids, as well **5**, can be converted into gold carbene complexes **6** by sequential deprotonation and coordination, opening the way for in situ catalyst tailoring.

Scheme 7



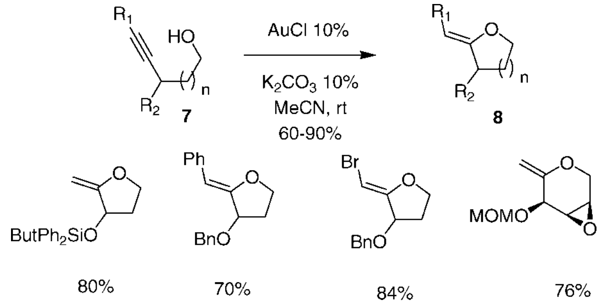
The hydration of phenylacetylene can also be carried out in aqueous media by using as catalysts a variety of gold(I) complexes containing the water-soluble phosphine ligands TPPMS, TPPDS, and TPPTS (mono-, di-, and trisulfonated triphenylphosphine, respectively).[44] The gold(I) alkynyl complexes [AuC′CR(TPPTS)] (where R = ^{t}Bu and 3-thiophenyl) give the highest ever reported turnover frequencies (1000 and 1060 h^{-1}, respectively) for the hydration of phenylacetylene under optimum conditions (0.1 mol % catalyst loading, 10 mol % H_2SO_4, 1 h reflux in 5:1 $MeOH/H_2O$). Recycling of the gold catalyst without significant drop of activity for at least three cycles has been achieved by using only water as a reaction medium. DFT calculations were used to compare relative energies of possible intermediates involved in the catalytic cycle.

An up to date application of cationic gold-catalyzed hydration of triple bond in the total synthesis of pterosines has been reported by Wessig and Teubner.[45] Furthermore, the remarkable alkynophilicity exhibited by $AuCl_3$ encouraged the exploration of the utility of propargyl glycosides as glycosyl donors.[46]

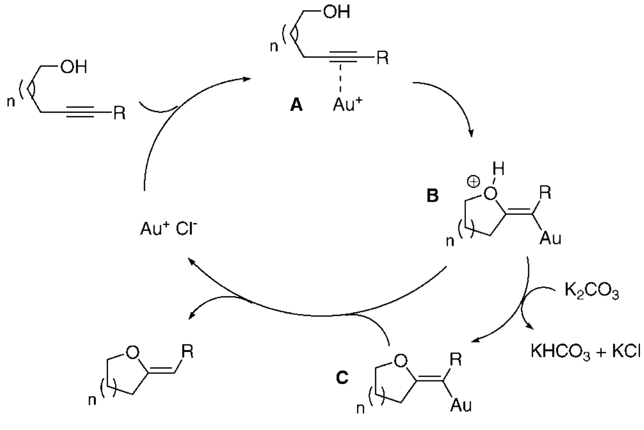
The intramolecular addition of an hydroxyl group to a carbon−carbon triple bond found many synthetic applications. ω-Acetylenic alcohols **7** have been regio- and stereoselectively converted to the corresponding α-alkylidene oxygenated heterocycles **8** in the presence of catalytic amounts of AuCl and K_2CO_3 (Scheme 8).[47]

Cyclizations of acetylenic alcohols are usually performed through metal catalysis and can yield to products resulting

Scheme 8



Scheme 9

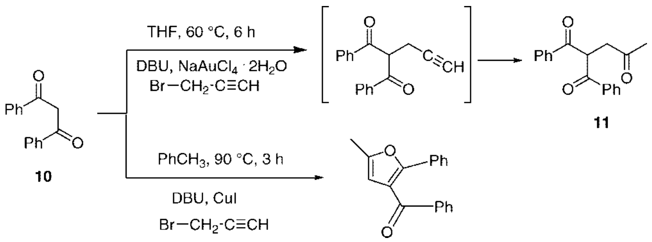


either from an exo-dig or an endo-dig process or from both. Intramolecular oxymercuration starting from acetylenic alcohols, usually led to the corresponding exocyclic enol ether.[48] The palladium(II)-catalyzed version was pioneered by Utimoto et al., but mixture or exo- and endo-dig products could be obtained.[49] Silver carbonate catalyzed the exclusive and very effective formation of exocyclic enol ethers.[50] Chromium, tungsten, and molybdenum catalysts led in the presence of base to endocyclic enol ethers,[51] while iridium(I) in methanol led to adducts derived from exocyclic products.[52] The Au-catalyzed cyclization of acetylenic alcohols is a general process because terminal, as well as nonterminal alkynes, functionalized or not, could be cyclized. Nevertheless, the role of a propargylic substituent appeared to be a key factor. The observed regio- and stereoselectivity suggest an activation of the acetylenic moiety through Au(I)-coordination (**A** in Scheme 9), which would induce a nucleophilic addition of the alcohol group in an anti-auration process.

The cyclization would lead to a protonated alkoxyorganogold intermediate **B**. Potassium carbonate probably deprotonated this intermediate leading to a neutral organogold species **C**. Hydrolysis of the carbon−gold bond would then liberate the α-alkylidene heterocycle and regenerate the gold catalyst. The fact that only catalytic amount of potassium carbonate is necessary suggests that the deprotonation as well as the carbon−gold bond hydrolysis are linked in the later step.

Gold catalysts have been proven to be remarkably useful agents for the selective addition reaction of an oxygen nucleophile over an alkyne moiety in the presence of other reactive functional groups. Sequential alkylation/regioselective gold-catalyzed hydration of the 1,3-dicarbonyl **10** with propargyl bromide led to the tricarbonyl derivative **11** (Scheme 10).[53] The unique catalytic behavior of the gold catalysis can be highlighted by the observation that under similar reaction conditions β-dicarbonyl compounds in the presence of a catalytic amount of CuI give 2,3,5-trisubstituted furans through sequential alkylation/cyclization/isomerization reactions.

Scheme 10

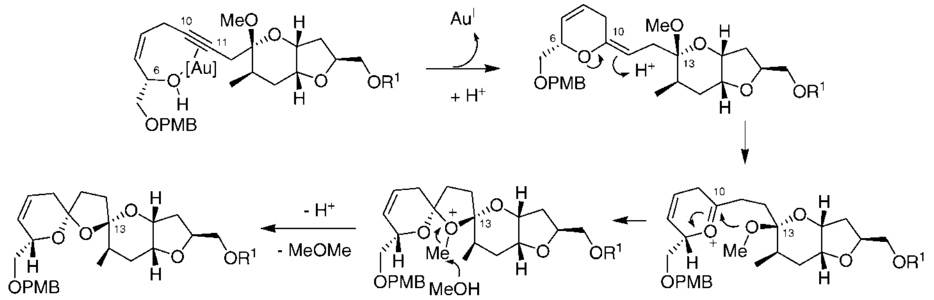


Forsyth and colleagues reported the use of gold chloride as a catalyst in a short and efficient alternative synthesis of part of a naturally occurring azaspiracid,[54] a member of a family of marine toxins that was found to be the cause of human poisoning in The Netherlands.[55] By contrast with the previously reported syntheses,[56] the gold-catalyzed assembly of a portion of the azaspiracid molecule was straightforward. The crucial step is represented by the formation of two molecular rings in a gold chloride-catalyzed reaction (Scheme 11). The mechanism of this elegant dual cyclization reaction is proposed to involve the initial formation of a complex between gold chloride and an alkyne in the precursor molecule. This renders the alkyne prone to chemical attack from an adjacent, strategically positioned hydroxyl group (OH), initiating the sequence that results in the formation of two rings with a spiro configuration, that is, twisted like a spiral staircase. The creation of such molecular complexity in a single step is extraordinary and provides a clear demonstration of how far gold chemistry has come.

Homopropargylic ethers with pendent nucleophiles, when subjected to Au catalysts in aqueous solvent, provided heterocyclic ketones.[57] The reactions are efficient, tolerant of functionality and ambient atmosphere, and operationally simple. Diastereoselectivity can be predicted on the basis of product thermodynamics. To ensure smooth alkyne hydration, water-saturated CH_2Cl_2 was used as the solvent. On the basis of the ability of simpler gold species to effect some of the elementary steps in this sequence, $NaAuCl_4$ was employed as the catalyst for many transformations. Reactions proceeded most smoothly and reproducibly when heated to 35 °C. Although $NaAuCl_4$ is a suitable catalyst for many reactions, the $Ph_3PAuCl/AgSbF_6$ system produced a more active catalyst that was preferable for slower reactions. Ag(I) serves to abstract the chloride from the Ph_3PAuCl, forming a more electrophilic catalyst. The sequence in Scheme 12 has been proposed as a mechanism for the process. Gold-mediated hydration of the alkyne **12** provides ketone **13**. Methanol elimination yields enone **14**, which undergoes metal-promoted conjugate addition to produce the cyclized product **15**. In support of this mechanism, small amounts of **13** have been isolated in reactions that were stopped at partial conversion, and then formation of cyclized derivative **15** has been observed when **13** was resubjected to the reaction conditions.

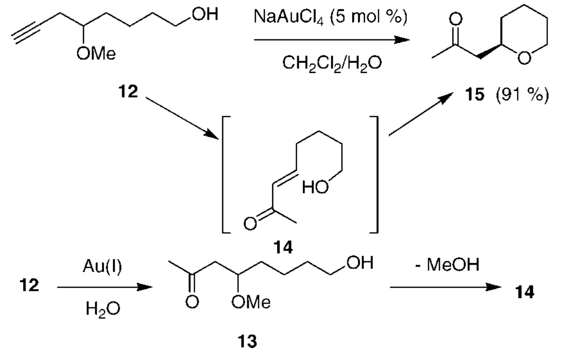
Although 1,4-additions of heteroatom nucleophiles into α,β-unsaturated carbonyl compounds normally require significantly harsher conditions, transition metal catalysis has been shown to facilitate the process.[58] A supporting role for trace amounts of HCl, formed through the reaction of the gold catalyst with H_2O, cannot be rigorously excluded, but

Scheme 11

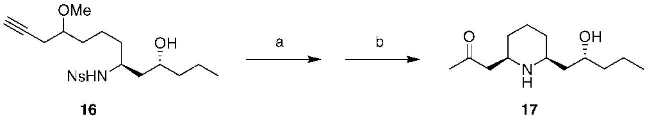


R^1 = TBDPS

Scheme 12

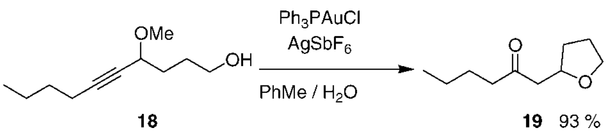


Scheme 13



(a) Ph$_3$PAuCl, AgSbF$_6$, PhMe, H$_2$O, 40 °C, 24 h, 89 %. (b) PhSH, K$_2$CO$_3$, CH$_3$CN, 95 %.

Scheme 14



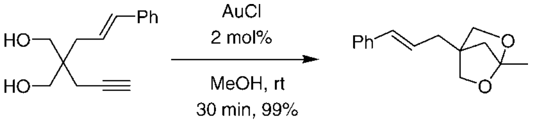
reaction of **12** with dilute HCl in CH_2Cl_2 led to no reaction. The method has been also applied to the preparation of nitrogen-containing heterocycles and to an efficient total synthesis of the natural product andrachcinidine **17** (Scheme 13).[59]

The ability to apply the mild gold-mediated cyclization conditions to internal alkynes dramatically enhanced the scope of products that can be accessed through the gold-mediated heterocycle synthesis. Exposing propargylic ether **18** to the standard cyclization protocol provided tetrahydrofuran **19** in 93% yield within 1 h (Scheme 14). This result clearly demonstrates that internal alkynes can be used as substrates in this reaction and also indicates that any gold-mediated reaction that yields an α,β-unsaturated carbonyl group can potentially serve as an entry into heterocycle synthesis.

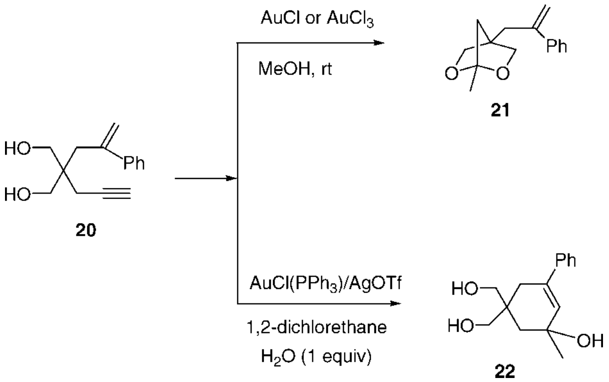
Genêt and co-workers have reported a very mild gold-catalyzed cyclization of bis-homopropargylic diols to the corresponding bicyclic ketals regioselectively (Scheme 15).[60]

Interestingly, the divergent reaction outcome of bis-homopropargylic diols **20** can be directed by a suitable choice of the solvent and the catalytic systems. The highly Lewis acidic gold cations favor the carbocyclization derivative **22** rather than oxycyclization product **21**(Scheme 16).[61]

Scheme 15



Scheme 16

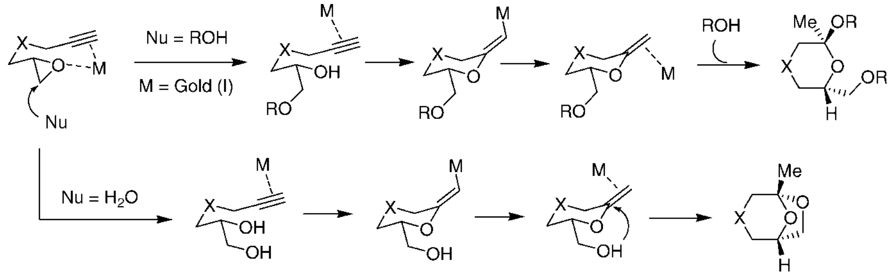


Shi and co-workers developed a novel access to ketal skeletons that are found in a number of biologically active natural products through highly regio- and diastereoselective intermolecular addition of water and alcohols to alkynyl epoxides catalyzed by $(Ph_3P)AuCl/AgSbF_6$(Scheme 17).[62] This procedure could involve a domino three-membered ring-opening, 6-exo-cycloisomerization, and subsequent intra- or intermolecular nucleophilic addition to a double-bond sequence. In addition, the high regio- and diastereoselectivities and mildness of these reaction conditions should make this reaction a valuable tool for synthesis of 2,6-trans-substituted morpholines. These latter derivatives were obtained in 44−70% yields by using $(PPh_3)AuCl/AgSbF_6$/*p*-TsOH in ethanol, prop-2-en-1-ol, or propan-2-ol. It was shown that *p*-TsOH was beneficial to both ring-opening of oxirane and hydroalkoxylation of double bond.

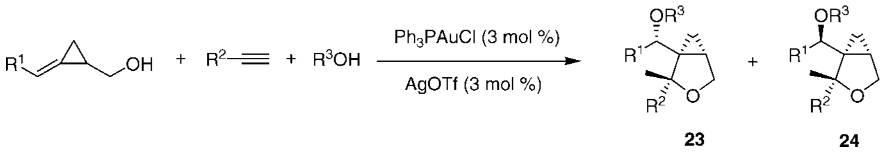
Moreover, catalyzed by gold(I), (*E*)- and (*Z*)-2-(arylmethylene)cyclopropylcarbinols, terminal arynes, and alcohols underwent three-component addition reactions to produce 3-oxabicyclo[3.1.0]hexanes **23**−**24** in high yields and moderate diastereoselectivities under mild conditions (Scheme 18).[63]

A plausible mechanism based on an intermolecular tandem hydroalkoxylation/Prins-type reaction pathway has been proposed (Scheme 19). Previously, Barluenga et al. found a novel tandem 6-exo-cycloisomerization/Prins-type cyclization of allyl-substituted 5-hexyn-1-ol derivatives catalyzed by gold and platinum complexes to give eight-membered carbocycles,

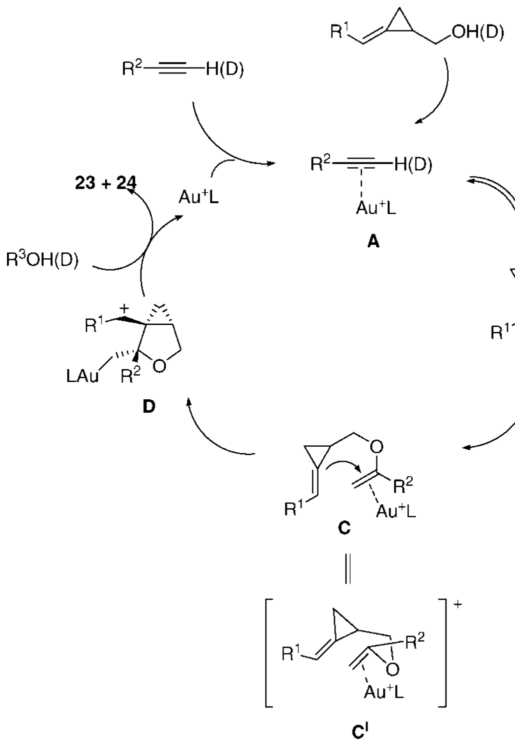
Scheme 17



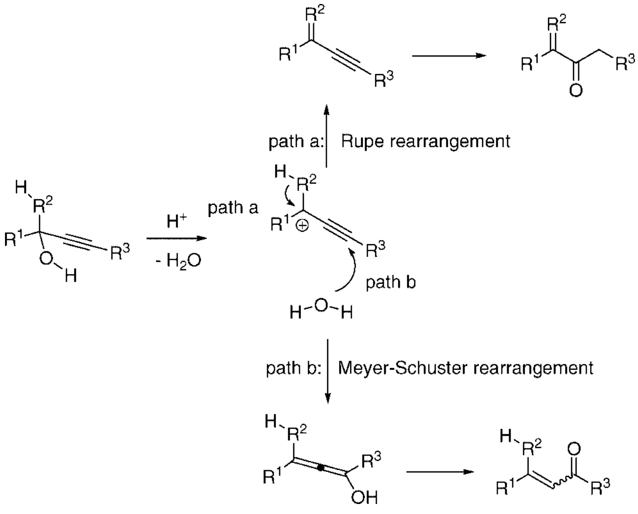
Scheme 18



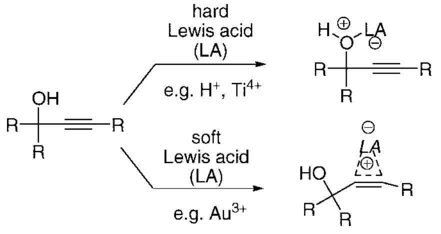
Scheme 19



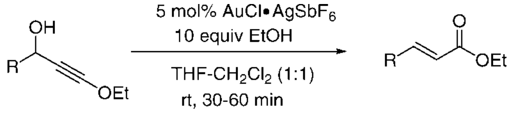
Scheme 20



Scheme 21



Scheme 22



indicating that enol ether could act as an acceptor for a Prins-type transformation.[64]

The Rupe and Meyer–Schuster rearrangements[65] are not often used in chemical synthesis because of harsh conditions and poor selectivity. The Meyer–Schuster products (Scheme 20, path b) are especially rare because the dehydration that leads into the Rupe pathway (Scheme 20, path a) generally takes precedence under traditional modes of activation that target the substrate through the alcohol moiety (i.e., acidic catalysts).

Soft activation of the alkyne by gold is likely to be more tolerant of sensitive functionality than hard activation of the oxygen atom and provided complementary selectivities (Scheme 21).

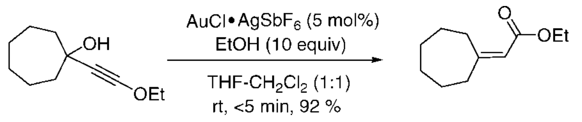
α,β-Unsaturated esters were prepared from ethoxyalkynyl carbinols using cationic gold catalysts (Scheme 22).[66] Substitution on the alcohol substrate, including aryl, alkyl, and vinyl groups, is well tolerated, with aliphatic substituents providing the highest stereoselectivity. Neither Rupe-type elimination products (from loss of water) nor β-hydroxy ester products (from addition of water) were observed.

The experiment illustrated in Scheme 23 demonstrates the applicability of these conditions to the synthesis of α,β-unsaturated esters from tertiary alcohols.

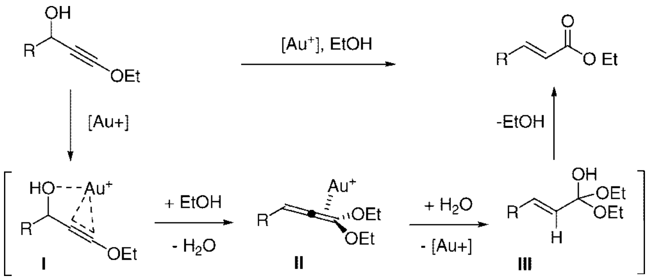
The mechanism is outlined in Scheme 24.

The pursuit of synthetic efficiency stimulated the design and development of new concepts and innovative synthetic strategies by implementing reaction cascades. The vast majority of the reported cascade sequences employ a single

Scheme 23



Scheme 24



starting material containing multiple functional groups strategically positioned along a chain, terminating with an alkyne functionality. In this context, gold(I)-catalyzed cyclization of alkynoic acids have been exploited as the first step in a sequence leading to an *N*-acyl iminium ion cyclization resulting in the formation of complex multiring heterocyclic products of the general structure.[67] Indeed, the treatment of a toluene solution of 1 mol % $AuPPh_3Cl/AgOTf$ with alkynoic acid **25** (1.0 equiv), followed by pyrrolyl ethyl amine **26**, lead to keto to keto amide **27** in 71% yield. The subsequent conversion from **27** to **28** by Au(I) required higher temperatures to surmount the activation barrier to the *N*-acyliminium ion. Accordingly, the reaction sequence was allowed by using toluene at reflux (Scheme 25).

2.3. Hydrocarboxylation of Alkynes

The group of Genêt reported the first example of a AuCl catalyzed cyclization of activated acetylenic acids **29** under mild reaction conditions, leading functionalized lactones **30** (scheme 26).[68] Interestingly the reactions did not need any additive and also $AuCl_3$ gave comparable yield on model reaction. The cyclization proceeded smoothly in a 5-exo-mode and tolerates a variety of α-substituents in the starting material.

At the same time, Pale and co-workers used a similar approach to synthesize different ring-sized lactones from unactivated ω-acetylenic acids.[69] The authors used a straightforward trick to boost the nucleophilicity of carboxylic group: a catalytic amount of potassium carbonate to generate the corresponding carboxylate anion. The cycloisomerization of γ- and δ-acetylenic acids catalyzed by AuCl was chosen to examine the regioselectivity and the limitations of the process.[70] The intramolecular cyclization of γ- or δ-acetylenic acids can afford both the exo- and endo-derivatives. Uchiyama et al. have reported a regiocontrolled intramolecular 6-endo-dig cyclization of γ-acetylenic acids mediated by acid catalyst.[71] By contrast, the exo-dig mode of cyclization predominated in the gold-catalyzed cycloisomerization reaction affording the lactones **32** and **34** as the major products and as a single stereoisomer **Z** (Scheme 27).

The cyclization of γ-acetylenic esters **35** is in the presence of $AuCl_3$ yields exclusively the isocoumarins **36** (Scheme 28).

2.4. Gold-Catalyzed Reactions of Alkynes Bearing a Proximate Oxygen Nucleophile

Propargylic[72] and homopropargylic *tert*-butyl-carbonates[73] **37**and *tert*-butyl-carbamates[74] **39** cyclize under mild reaction conditions in a selective 5-exo-dig or 6-exo-dig fashion in the presence of a cationic gold(I) complex. A study concerning the Au(I)-catalyzed rearrangement of propargylic *tert*-butyl carbonates containing proximate internal alkyne moiety into 4-alkylidene-1,3-dioxolan-2-ones has been described.[72] 5-Endo-dig cyclization of *N*-alkynylcarbamates to give oxazolinones have been reported.[74b] These cyclizations proceeded readily at room temperature or even lower temperatures and are characterized by low catalyst loading, mild conditions, and operational simplicity (Scheme 29).

Mechanistically, it is interesting to note that the nucleophilic oxygen atom reaches the distal position of the alkyne because the coordination of the catalyst on the alkyne should bend the latter on the sense shown by both donation and back-donation and thus reduce this distance (Scheme 30, intermediate **A**). After the nucleophilic attack, intermediate **B** fragments and delivers **C**, isobutene, and the proton, which is necessary for the final protodeauration step to led to the reaction product and regenerate the catalyst.

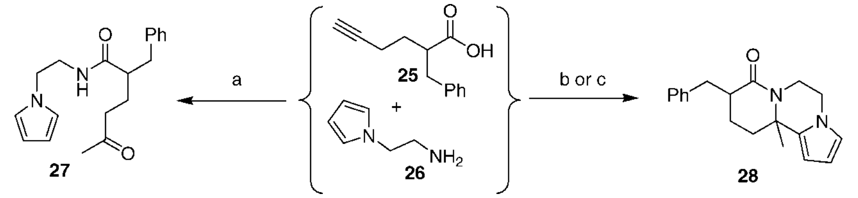
In agreement with this mechanistic hypothesis, alkyne-substituted *N*-Boc-protected alkynylamines reacted similarly to the parent substrate **39**, providing the corresponding oxazolidinones with complete (*Z*)-stereoselectivity regardless of the electronic character of the alkyne substitution.[74d] Gold(I)-catalyzes an efficient tandem cyclization of tert-butyl carbonate derivatives of hex-1-en-5-yn-3-ol **41** where nucleophilic participation of the O-Boc group appears to intercept a carbocationic (or cyclopropyl carbene) Au intermediate.[75] The protocol leads to densely functionalized cyclohexene-3,4-diol derivatives **42** where 1,2- or 1,2,3-stereocenters are controlled in a highly diastereoselective fashion (Scheme 31).

Gold-catalyzed reactions of oxo-alkynes have been recently reviewed by Yamamoto.[76] An interesting branch of this chemistry involve the intramolecular attack of a carbonyl group on an alkyne to form a pyrylium intermediate, which can further react with a suitable dienophile such as an alkyne, to form naphthalenes by means of a [4 + 2] cycloaddition, followed by a cycloreversion. The proposed mechanism for this formal [4 + 2] benzannulation involve the coordination of the triple bond to AuX_3 followed by the intramolecular nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne to give the pyrylium intermediate. The Diels−Alder type cycloaddition with the alkyne provide an unstable bridged tricyclic intermediate. The subsequent bond rearrangement affords the naphthalene derivative and regenerates the catalyst (Scheme 32).

$AuBr_3$ is the catalyst of choice for this transformation. Interestingly, the reaction can also be catalyzed by heterogeneous gold-supported catalysts.[77] Gold nanoparticles supported on metal oxides and activated carbon are able to catalyze the benzannulation reaction of *o*- (phenylethynyl-)benzaldehyde and phenylacetylene to 1-benzoyl-2-phenylnaphtalene with high selectivity at 99% conversion. The heterogeneous catalytic system can be reused several times without loss of activity or selectivities.

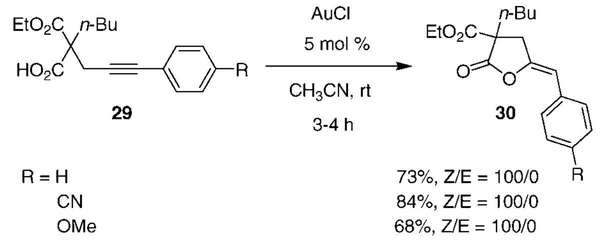
In the last four years, this chemistry has been comprehensively studied by several groups.[78] For example, a new elegant application to the total synthesis of *rac*-3-desoxyequilenin and a chrisenone derivative has been reported by

Scheme 25[a]

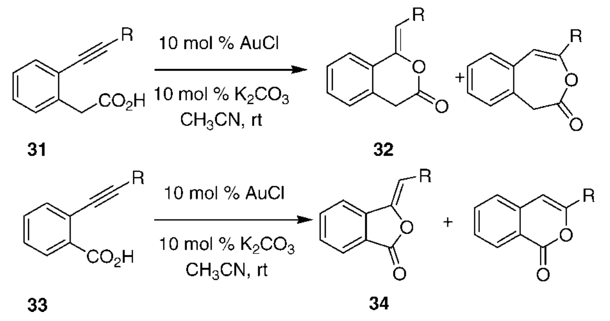


[a] Reaction conditions: (a) AuPPh3Cl/AgOTf (1 mol %), toluene, rt, 71%; (b) AuPPh3Cl/AgOTf (1 mol %), toluene, reflux, 68%; (c) AuPPh3Cl/AgOTf (1 mol %), toluene, rt, 3 h then reflux, 2 days, 81%.

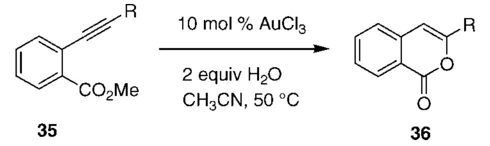
Scheme 26



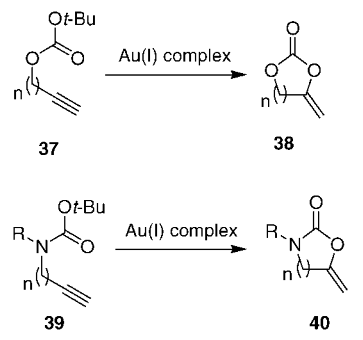
Scheme 27



Scheme 28

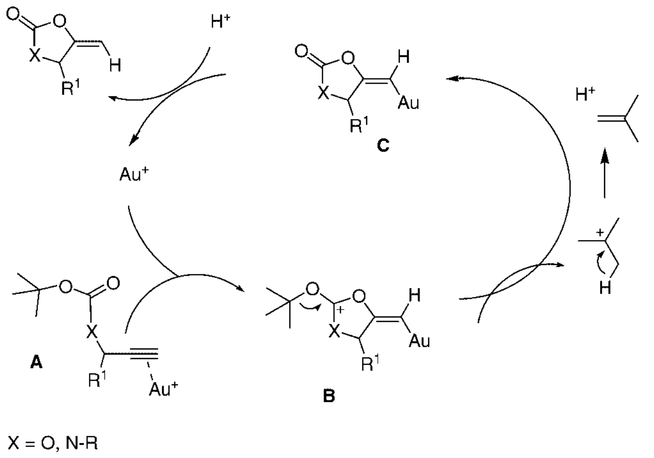


Scheme 29

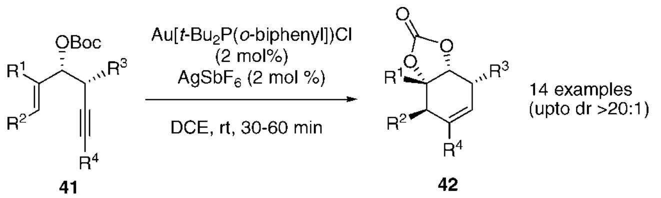


Dyker and Hildebrandt.[79] The strategy has been recently extended to benzenediazonium 2-carboxylate as benzyne precursors to afford functionalized anthracene derivatives.[80] Interestingly, in this case, AuCl was found to be the best catalyst for this transformation. Moreover Asao report the full details of the extension of this approach to other dienophiles as carbonyl compounds which produces aromatic ketones and benzofused heteroaromatic compounds (Scheme 33).[81]

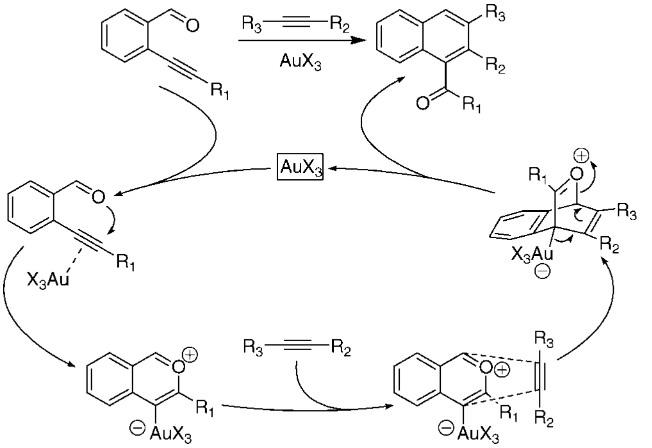
Scheme 30



Scheme 31



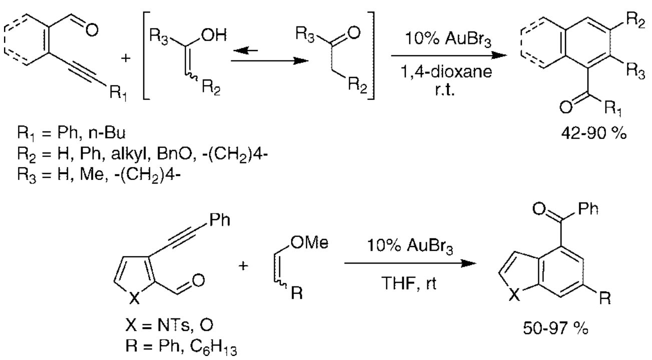
Scheme 32



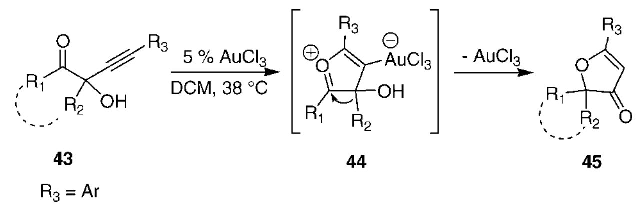
Kirsch and co-workers reported a new approach to highly substituted and 3(^{2}H)-furanones **45** by a gold-catalyzed cyclization/1,2-migration cascade.[82] An oxonium intermediate **44**could be involved in the reaction mechanism. Whereas gold(I) and silver(I) complexes failed, $AuCl_3$ gave excellent results under mild temperature. It is interesting to note that when R_1 and R_2 are part of a ring, the reaction leads to a ring contraction (Scheme 34).

More recently, two protocols for the construction of 4-iodo-3-furanones **47** through a sequence consisting of

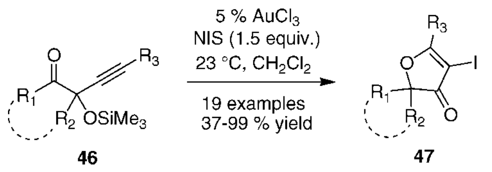
Scheme 33



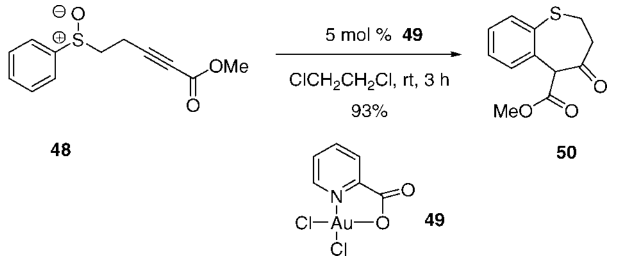
Scheme 34



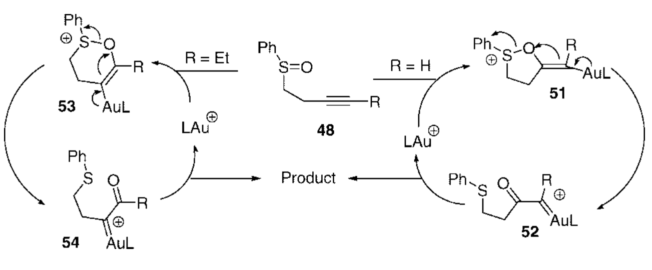
Scheme 35



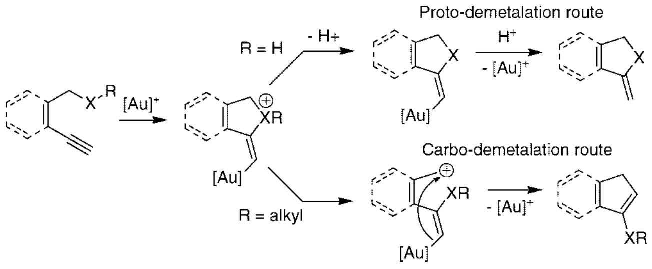
Scheme 36



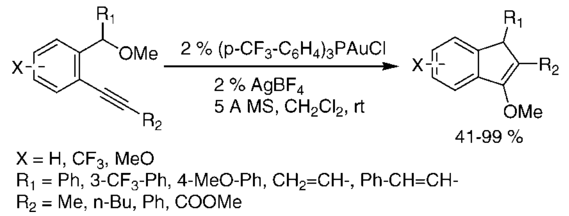
Scheme 37



Scheme 38



Scheme 39



cyclization and migration of 2-alkynyl-2-sylyloxy carbonyl compounds **46** were developed.[83] In one, electrophilyc cyclization is directly induced by *N*-iodosuccinimide (NIS). In the second less-limited variant, $AuCl_3$ catalyzes the reaction in the presence of NIS to provide highly substituted heterocycles in moderate to excellent yields (Scheme 35).

Zhang's and Toste's group independently discovered a novel Au-catalyzed intramolecular redox reaction of sulfinyl alkynes **48** (Scheme 36).[84]

A proposed mechanism for the gold-catalyzed rearrangement of homopropargyl sulfoxides is detailed in Scheme 37. Coordination of cationic gold(I) to the alkyne induces nucleophilic addition of the sulfoxide oxygen. When the alkyne is terminal or substituted with an electron-withdrawing group, 5-exo-dig cyclization of the nucleophile onto the internal carbon of the alkyne is favored, yielding intermediate **51**. On the other hand, when the alkyne is substituted with an alkyl group, **53** is generated by a 6-endo-dig cyclization. After cyclization, gold(I)-assisted sulfide release produces gold-carbenoid intermediate **52** or **54**. The α-oxo-Au carbenoid generated in this reaction can efficiently cyclize the benzene ring to give the product.

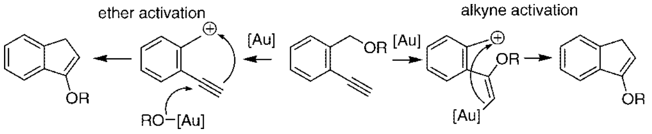
One of the more fascinating work in the field of gold promoted alkyne activation has been published by Toste and Dubé.[85a] The key idea was that in the gold-catalyzed addiction of nucleophiles to triple bond, the proto-demetalation of the vinylgold intermediate might be circumvented through intramolecular reaction with an in situ generated electrophile. Toward this goal, the authors envisioned that a benzylic cation, a potent electrophile, could be generated by cyclization-induced fragmentation of a C−X bond (Scheme 38).

The best reaction conditions to achieve this objective were found using a strong electrophilic gold complex such as $(p\text{-}CF_3{-}C_6H_4)_3PAuBF_4$ in dichloromethane in the presence of activated molecular sieves to freed the reaction environment from water and avoid any parasite hydrolytic process (Scheme 39).

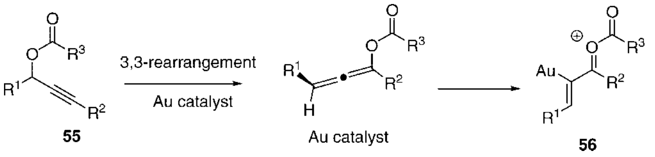
The mechanism was elegantly elucidated by a double label crossover experiment and performing a reaction with an enantio-enriched substrate. The lack of observed crossover and the excellent chirality transfer are consistent with a intramolecular mechanism involving alkyne activation followed by C−O bond scission to generate a carbocation that is trapped by the vinylgold(I) intermediate to give the observed indene adduct, rather than an alternative Lewis acid promoted ionization of benzylic ether, followed by the trapping of the cation with the triple bond and the addition (concerted or stepwise) of the gold(I)-alkoxide to the alkyne to afford the indenyl ether (Scheme 40).

A similar strategy has been applied to an efficient formation of 1-carboxycyclohexa-1,4-dienes and carboxyarenes through Au-catalyzed 1,5-enyne cycloisomerization involving carboxy group migration and Au-mediated C−C single bond formation.[85b] Propargylic,[86] as well as allylic, esters[87] and allenyl carbinol esters[88] served as versatile

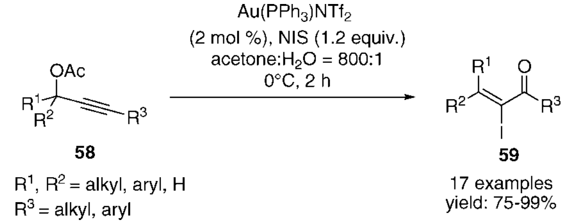
Scheme 40



Scheme 41



Scheme 42



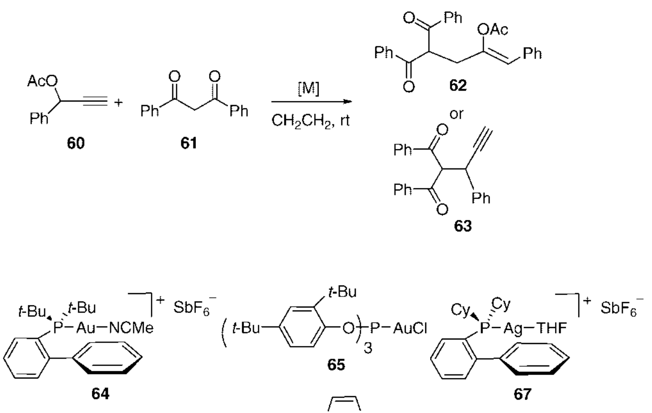
substrates for Au catalysis. Zhang's group reported 3,3-rearrangement of propargylic esters **55** and subsequent activation of the in situ generated carboxyallenes to form highly reactive Au-containing oxocarbenium intermediate **56** (Scheme 41).

Efficient synthetic methods for highly functionalized 2,3-indoline-fused cyclobutane,[89] cyclopentenones,[90] α-alkylidene-β-diketones,[91] and alkenyl enol esters/carbonates have been accomplished.[92] A notable observation in some of these studies is that the Au−C(sp^2) bond in **56** can react with intramolecular electrophiles[93] such as iminiums and activated acyl groups. Au−C(sp^2) bond could also react with electrophilic iodine intermolecularly, leading to efficient formation of α-iodoenones upon hydrolysis. Indeed, an efficient synthesis of linear α-iodoenones **59** from readily accessible propargylic acetates **58** was developed.[94] The reaction works well not only with substrates derived from aldehydes but also with those from ketones. Good to excellent *Z*-selectivities were observed in the case of aliphatic propargylic acetates.

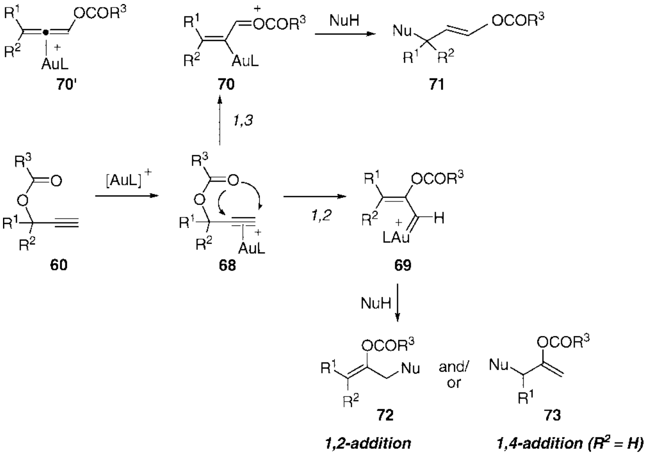
A simple procedure for the formation of functionalized enol carboxylates under mild conditions through gold-catalyzed addition of carbon nucleophiles to propargyl carboxylates has been developed by Echavarren's group.[95] It is worth noting that in contrast with oxophilic Lewis acids that lead to nucleophilic substitution with propargyl carboxylates, Au(I) promotes the nucleophilic addition to these substrates. Indeed, they tested the reaction of propargyl acetate **60** with 1,3-diketone **61** in the presence of AuCl, $AuCl_3$, cationic Au(I) complex **64**, a prectalysts **65** and **66**, and cationic Ag(I) complex **67** (Scheme 43).

The addition of **61** to **60** proceeded at room temperature to give enol acetate **62** with all the gold catalysts. A mixture of *E* and *Z* isomers was obtained with AuCl and $AuCl_3$, whereas cationic Au(I) catalysts provided pure *Z*-**62**. The reaction was faster and cleaner with complex **64**. With **66** and Ag(I), a mixture of **62** and the product of nucleophilic substitution **63** was obtained. Reaction of **60** with cationic complex **67** or $Sc(OTf)_3$ as catalysts gave acetylene **63**, whereas with $Cu(OTf)_2$, a mixture of **63** and the product of hydration of the alkyne (2-benzoyl-1,3-diphenylpentane-1,4-dione) was obtained. With AgSbF6 (5 mol %), this trione was obtained in 97% yield. These results are consistent with the mechanistic hypotheses shown in Scheme 44 in which the enol of the 1,3-dicarbonyl compound or the arene adds to intermediates **69** or **70** [complexes **70** can be also depicted as Au(I)-coordinated allenes **70′**] (Scheme 44). Although the factors that control the regioselectivity of the addition are still not totally understood, propargyl carboxylates bearing phenyl or *gem*-dimethyl groups at C-3 lead to products **72** of 1,2-addition to α,β-unsaturated Au(I) carbenes **69**, whereas propargyl carboxylates with a methyl group or no substituents at that position give adducts **71**or **73**.

Scheme 43



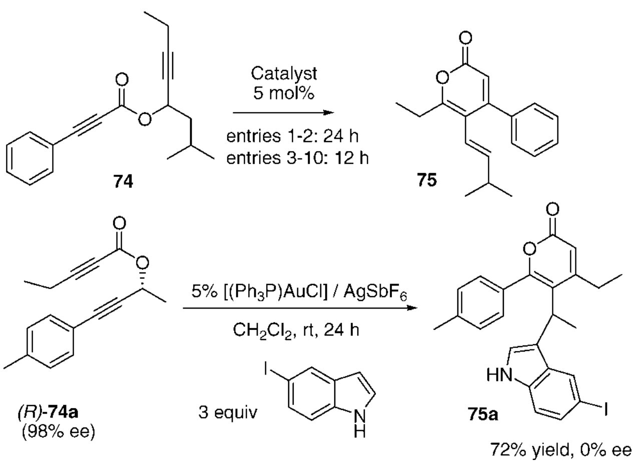
Scheme 44



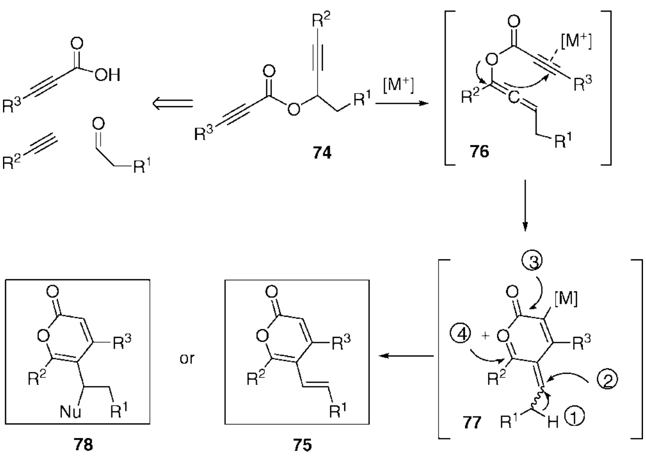
Convergent syntheses[96] of α-pyrones have traditionally involved the lactonization of ketoesters.[97] Transition-metal catalyzed cycloaddition[98] and annulation reactions[99] are recent alternatives that have attracted much attention, but most are limited by the resulting poor regioselectivity or the requirement for harsh reaction conditions. The readily accessible propargyl propiolate **74** could be converted to different complex α-pyrones **75** by a gold-catalyzed cascade process (Scheme 45).[100]

The [3,3]-sigmatropic rearrangement of **74** catalyzed by gold would generate an enyne allene **76**. A 6-endo-dig cyclization would be induced by the activation of the alkyne moiety in **76** to give the oxocarbenium intermediate **77**. In one possible pathway, elimination (Scheme 46) would afford a vinyl α-pyrone **75**. The intermediate **77**could also be trapped by a variety of nucleophiles. The trapping of electrophilic intermediate **77**, which can in principle be

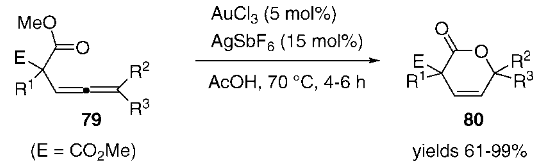
Scheme 45



Scheme 46



Scheme 47



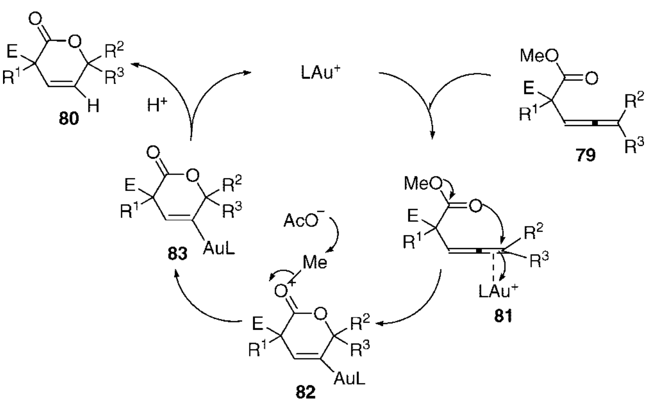
attacked at three distinct sites could be controlled by using different nucleophiles and reaction conditions.

A new efficient route to β,γ-unsaturated δ-lactones **80** by means of a gold-catalyzed intramolecular nucleophilic attack of a carboxy ester on an allene has been developed by Băckvall and co-workers (Scheme 47).[101]

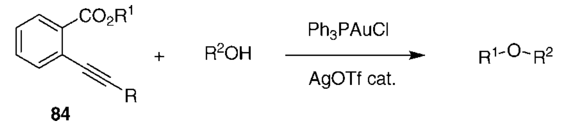
It is worth noting that the starting derivatives **79** undergo only carbocyclization reactions under palladium catalysis.[102] The proposed mechanism for the formation of compounds **80** is shown in Scheme 48. The allene is activated by coordination to cationic gold and undergoes intramolecular nucleophilic attack by the carbonyl oxygen of the ester group to form the cyclic cationic species **82**, which is demethylated by action of the solvent to produce the neutral vinyl-gold intermediate **83**. Protonolysis of the gold−carbon bond in **83** affords lactone **80** and regenerates the cationic gold catalyst.

A new catalytic, practical etherification method of alcohols with a designed *ortho*-alkynylbenzoic acid alkyl ester **84** as an effective alkylating agent has been developed (Scheme 49).[103]

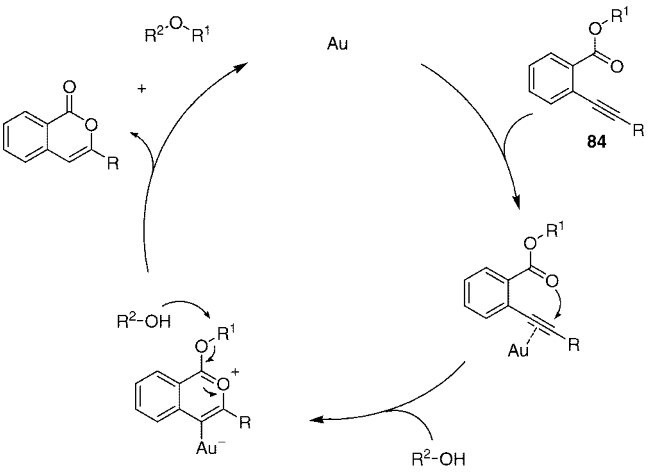
Scheme 48



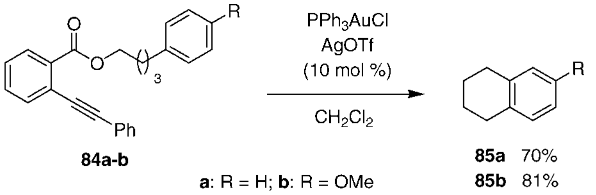
Scheme 49



Scheme 50



Scheme 51



The reaction likely proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack of alcohols according to a mechanism illustrated in Scheme 50.

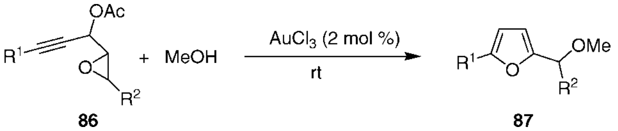
The synthetic utility of the protocol is further enhanced by its ability to promote the Friedel−Crafts alkylation under mild conditions (Scheme 51).

An efficient approach to 2,5-disubstituted furans **87** has been developed by utilizing gold-catalyzed sequential nucleophilic attack onto esters of 1-alkynyl-2,3-epoxy alcohols **86** with complete regioselectivity (Scheme 52).[104]

2.5. Hydroamination of Alkynes

Catalytic additions of ammonia or primary and secondary amines to nonactivated alkenes and alkynes are called

Scheme 52



86 **87**

hydroaminations. These reactions of fundamental simplicity represent the most atom efficient processes for the formation of amines, enamines, and imines, which are important bulk and fine chemicals or building blocks in organic synthesis. Consequently, the development of corresponding hydroamination reactions has received much attention.[105] Hydroaminations of alkynes can only be achieved in the presence of certain catalysts.[106] It is also important to understand that alkynes undergo hydroamination reactions more easily than alkenes. Gold complexes have attracted intense interest for the development of environmentally benign alternative routes of hydroamination of unactivated alkenes, alkynes, allenes, and 1,3-dienes.[107]

Since the first example of gold-catalyzed hydroamination by Utimoto,[108] intramolecular hydroamination of alkynylamines has made significant progress. Indeed, gold catalysts accomplished the development of an alternative approach to indole scaffolds through gold-catalyzed cyclization reaction of 2-alkynylaniles **88** in ethanol or ethanol−water mixtures at room temperature (Scheme 53).[109]

Moreover, it was reported the gold-catalyzed cyclization/conjugate addition type reaction of 2-alkynylanilines **88** with α,*β*-enones **90** leading to the 3-alkylindoles **91** in moderate to high yields (Scheme 54).[110]

Usually, the reaction of **88** with **90** resulted in satisfactory yield at 30 °C. An equimolecular ratio of **88** and **90** were reacted. The reaction proceeds smoothly even with less reactive α,*β*-enones such as *β*-disubstituted α,*β*-enones and cyclic enones. Gold-catalyzed sequential cyclization/alkylation, *N*-alkylation/cyclization or *N*-alkylation/cyclization/alkylation reactions leading to different indoles have been directed by changing the 2-alkynylaniline **88** /α,*β*-enone **90** ratio and the reaction temperature. With the aim at developing a synthetic protocol involving the use of more environmentally benign solvents and avoiding the need of protecting groups and/or harsh conditions,[111] the gold-catalyzed annulation of 2-ethynylaniline derivatives to 2-substituted indoles have been also investigated in ionic liquid (Scheme 55).[112] Cyclization of 2-alkynylanilines in the presence of $NaAuCl_4 \cdot H_2O$ using $[bmim]BF_4$ as the reaction medium affords 2-substituted indoles in high yields ($[bmim]^+$ stands for the 1-butyl-3-methylimidazolium cation). The reaction times were significantly reduced using microwave irradiation.

The nature of the gold salt was found to play a pivotal role for the reutilization of the catalyst system. Only *n*-Bu_4NAuCl_4 was recycled and reused for more than five runs without any significant loss of catalyst activity. 2,3-Disubstituted indoles **91** can be prepared from 2-alkynylanilines **88** and 3-buten-2-one **90a** through a one-flask annulation/alkylation sequence and 1,2,3-trisubstituted indoles **93** is obtained from the same starting materials via an aza-Michael addition/annulation/alkylation process (Scheme 56).

A highly efficient double-hydroamination reaction of 2-alkynylanilines **88** with terminal alkyne **94** leading to *N*-alkenylindoles **95** was developed by using gold(III) as a catalyst under neat conditions (Scheme 57).[113] Other catalysts such as $In(OTf)_3$, $Y(OTf)_3$, and $Sn(OTf)_2$ were found to be ineffective in this reaction. Different solvents were also examined, and the best results were obtained without using any solvent.

A tentative mechanism for the gold(III)-catalyzed double hydroamination is proposed in Scheme 58. Terminal alkyne **94** is activated by $Au(OTf)_3$ to generate the intermediate **96**, which further reacts with **88** to yield the first hydroamination product **97**. Then the carbon−carbon triple bond of **97** is activated by $Au(OTf)_3$ again and produces the intermediate **98** via nucleophilic addition of the imine nitrogen. Finally, the C-3-position of indole is protonated to give the final product **95** and the catalyst is regenerated.

As for the intermolecular version, it was demonstrated that the combination of $(Ph_3P)AuCH_3$ and acidic promoters efficiently catalyzes hydroamination of alkynes with anilines (Scheme 59).[114]

The gold(I)-catalyzed intermolecular hydroamination of alkynes with aromatic amines appears to involve electrophilic attack of the amine to alkynes (Scheme 60).

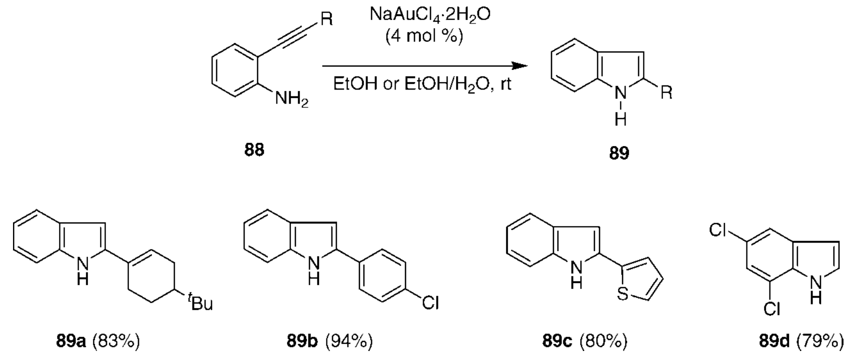
The cationic gold(I) species, $Au(PPh_3)^+$, generated by protonolysis of $(Ph_3P)AuCH_3$, has been envisaged to interact with an alkyne, forming a cationic Au(I)−alkyne complex **I**. Complex formation should be favored by an electron-donating substituent in the alkyne molecule, as was indeed observed. Two reaction pathways for an amine to react with the gold(I)−alkyne complex can be considered. One is direct intermolecular nucleophilic attack of the amine on the alkyne ligated to the gold center. However, this route has been considered less likely since an aniline that has a more electron-withdrawing substituent reacts faster. The other route, involving coordination of the amine to the gold center (intermediate **II**) prior to the C−N bond formation, appears more probable. Aliphatic terminal alkynes displayed reactivities similar to aromatic alkynes. Internal ones, less reactive presumably because of steric reasons, required longer reaction times to obtain acceptable yields. It is interesting to note that phenylhydrazine also added to phenylacetylene, affording a high yield of the corresponding phenylhydrazone. Despite the tremendous effort made, aliphatic amines did not add to alkynes under conditions similar to the aniline reactions. The catalytic activity of gold(I) catalyst resulted much higher than that observed with the other catalyst systems previously reported.[115] The findings helped to overcome the drawbacks of the procedure involving aminomercuration of alkynes, followed by demercuration.[116]

Amines were obtained in high yields via a gold-catalyzed hydroamination of alkynes followed by reduction (Scheme 61).[117]

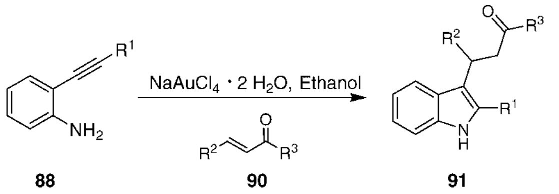
Interestingly, gold nanoparticles on a polysaccharide-based support (chitosan) were found to catalyze with very high yields the regioselective hydroamination of alkynes without the need for acid promoters and inert atmosphere. The metal−support interactions were studied by Raman, IR, UV, and NMR spectroscopy. The interaction between gold and the NH and OH groups of chitosan allow good dispersion of the nanocrystals on the biopolymer. The chitosan−silica composite further stabilizes gold nanoparticles against agglomeration or leaching compared with other supports.[118]

A method to efficiently prepare substituted 1,2-dihydroquinolines and quinolines by Au(I)-catalyzed tandem hydroamination−hydroarylation under microwave irradiation was developed.[119] This method requires short reaction time (10−70 min) and has a broad substrate scope (Scheme 62).

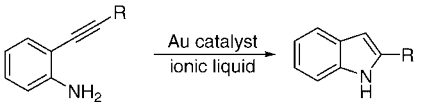
Scheme 53



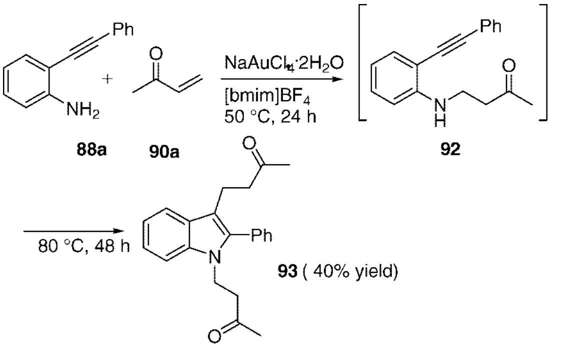
Scheme 54



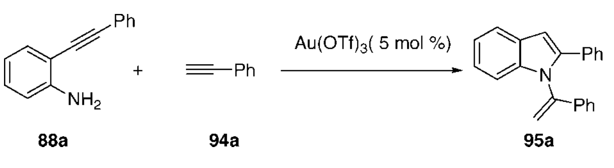
Scheme 55



Scheme 56



Scheme 57



The **100a**/AgOTf-catalyzed reactions of alkynes **94** with primary arylamines **99a**−**b** bearing an *o*-alkylcarbonyl or -arylcarbonyl group produced 2,4-disubstituted quinolines **103a**−**b** in 63−94% yields within 30 min (Scheme 63).

A study on the gold(I)-catalyzed intramolecular hydroamination of trichloroacetimidates derived from propargyl and homopropargyl alcohols has been described.[120] In the presence of 2−5 mol % of cationic Au(I) complex, a variety of trichloroacetimidates **104** undergo efficient hydroamination under an exceptionally mild condition. An orthogonality of the gold-catalyzed protocol with those using a stoichiometric electrophile has been demonstrated (Scheme 64).

The reactions with gold catalysts of several propargylic trichloroacetimidates have been studied. Only with the propargyl and the 1-methylpropargyl substituent was a selective cyclization observed (Scheme 65); with gold(III) chloride in acetonitrile, the product of a fast hydroamination to 4-methylene-4,5-dihydrooxazoles was obtained, and in chloroform, the slower subsequent aromatization could not be prevented which delivered the oxazoles after long reaction times.[121] With gold(I) catalysts in chloroform or dichloromethane selective hydroamination to 4-methylene-4,5-dihydrooxazoles without subsequent aromatization was exclusively observed.

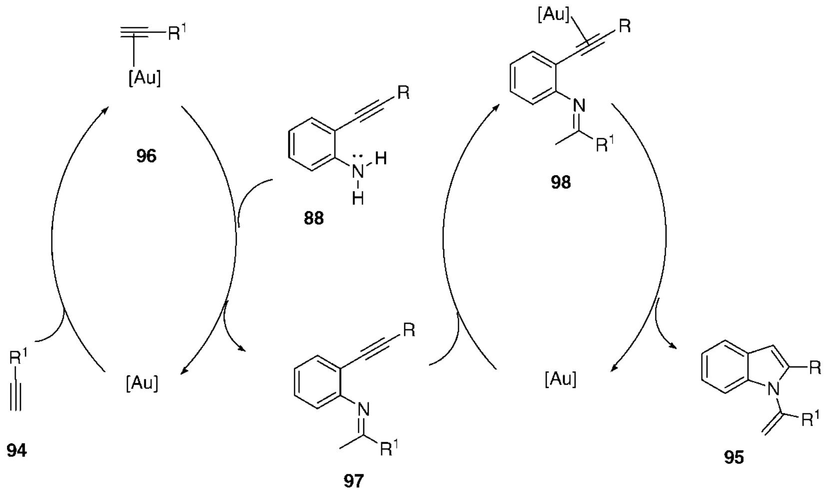
The gold(I) catalysts also allowed chemoselective cycloisomerization of *N*-propargylcarboxamides **107** to 5-methylene-4,5-dihydrooxazoles **108** (Scheme 66).

Upon treatment with catalytic amounts of gold(I) catalyst and a base cocatalyst, *O*-propargyl carbamates **109** smoothly undergo a 5-exo-dig cyclization at room temperature to afford 4-methylene-2-oxazolidinones **110** in high yield (Scheme 67).[122] Simple AuCl represented a highly efficient catalyst affording oxazolidone derivative in excellent isolated yield. It is noteworthy that it was possible to perform the reaction under air without any loss of catalytic activity. Substrates with a substituent at the alkyne terminus stereoselectively give rise to (*Z*)-4-alkylidene-2-oxazolidinones. The cyclization of *O*-propargyl carbamates to 4-methylene-2-oxazolidinones can be also performed under Cu^{2+} or Ag^{+} catalysis.[123] However, rather long reaction times and elevated temperatures are usually required.

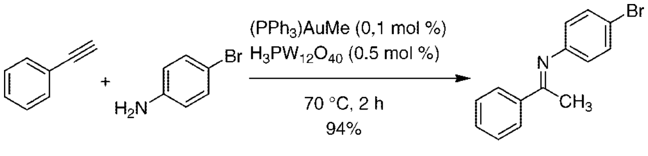
Gold(I)-catalyzed intramolecular hydroamination of *O*-propargyl-*N*-Boc-hydroxylamine **111** has been reported to give a novel, catalytic, and mild approach to 2,5-dihydroisoxazole derivatives **112** (Scheme 68).[124] After brief optimization with regard to ligand, counteranion, and solvent, $Au(PPh_3)OTf$ (5 mol%), generated in situ from the corresponding chlorogold complex and silver salts, was best suited for the current cyclization. However, in a reaction of **111a**, the desired dihydroisoxazole **112a** formed, along with a considerable amount of hydration byproduct because of adventitious water. By using 4 Å molecular sieves as additive, the hydration could be successfully suppressed. A similar 5-endo-dig process employed a combination of superstoichiometric I_2/K_2CO_3.[125] While the approach afforded a novel route to 4-iodo-functionalized 2,5-dihydroisoxazoles (3-isoxazoline), use of stoichiometric Lewis acid sets several limitations: (1) harsh conditions imposed by strong electrophilic I_2 (3 equiv) and (2) the protocol will not be applicable to olefinic substrates because the reagents favor the activation of alkene over alkyne.

The reactivity of gold was extended beyond the paradigm of electrophilic activation, and further reactions wherein gold serves both as a π-acid and as an electron donor have been developed. The reactivity by gold(I)-promoted addition of a

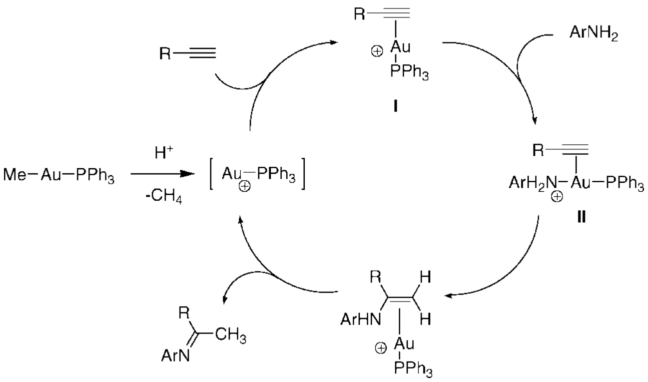
Scheme 58



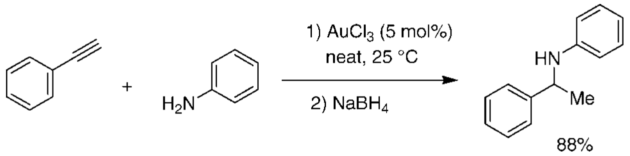
Scheme 59



Scheme 60



Scheme 61



leaving-group-bearing nucleophile to an acetylene with subsequent gold(I)-assisted loss of the leaving group have been exploited (Scheme 69).

Indeed, a modification of the Schmidt reaction[126] wherein alkyl azides **113** serve as nucleophiles toward gold(I)-activated alkynes with subsequent gold(I)-aided expulsion of dinitrogen allowed the synthesis of multiply substituted pyrroles **114** (Scheme 70).[127]

A highly efficient method for the preparation of synthetically useful tricyclic indole derivatives **116** having a substituent at the 3-position of the indole nucleus was established by sequential $AuBr_3$-catalyzed cyclization of *N*-(*o*-ethynylphenyl)imines **115**/[3 + 2]cycloaddition reactions (Scheme 71).[128]

The previously reported protocol for the preparation of 3-substituted tricyclic indoles **116** involved a stoichiometric amount of $W(CO)_6$ to bring the reaction to completion.[129] Although various metal complexes exhibit much higher catalytic activity than the tungsten carbonyl complex,[130] $PtCl_2$ and $AuBr_3$were found to be the best catalysts in terms of product yield and reaction time, respectively.

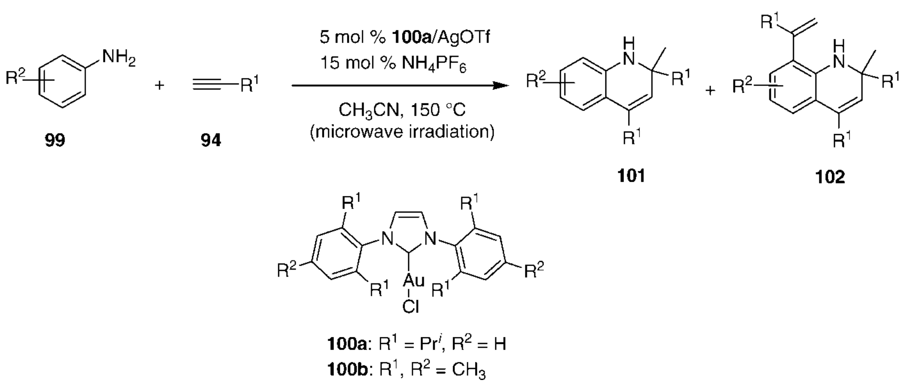
A cascade cycloisomerization of propargyl N-containing heterocycles **117** into various types of N-fused pyrrolo heterocycles **118** in the presence of gold catalyst has also been developed. The reaction proceeds via alkyne–vinylidene isomerization with concomitant 1,2-migration of H, silyl-, and stannyl groups, as well as previously unknown 1,2-migration of a germyl group, giving easy access to a variety of C-2-functionalized heterocycles (Scheme 72).[131]

Acetyloxy, diethylphosphatyloxy, and O-TBS-protected propargylic substrates **119** bearing alkyl, aryl, heteroaryl, and alkenyl substituents at the triple bond, as well as those possessing terminal alkyne moiety, underwent very smooth cycloizomerization in good to excellent yields (Scheme 73).[132] The cycloisomerization protocol appeared to be general with regard to the heterocyclic core: C-1,C-3-disubstituted indolizines, pyrrolo-quinoxalines, and pyrrolothiazoles can efficiently be synthesized from readily available precursors.

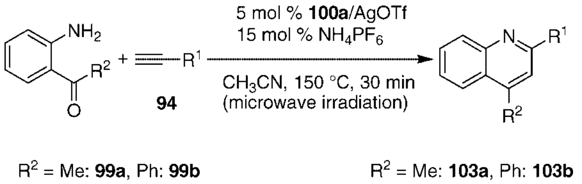
2.6. Gold-Catalyzed Addition Reactions of Sulfur Nucleophiles to Carbon–Carbon Triple Bonds

The fact that sulfur is generally poisonous toward transition metals seems to indicate a general incompatibility between the two.[133] Nonetheless, some novel and exciting gold-catalyzed additions of a diverse range of functionalized sulfur derivatives to alkynes, conjugated olefin systems, and allenes have been reported. Facile synthesis of benzothiophenes bearing a substituent at the C-3 position is of great interest because this structural framework is often seen in biologically active compounds.[134] In general, functionalization of the C-3 position is carried out by electrophilic substitution reactions.[135] However, lithiation at the C-3 position by using *sec*-BuLi is required prior to alkylation to attach an alkyl group, such as (α-alkoxy alkyl), benzyl, or allyl groups.[136] Interestingly, the gold-catalyzed cyclization of (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides, **121**, under mild conditions can give 2,3-disubstituted benzothiophenes, **122**, in excellent yields (Scheme 74).[137]

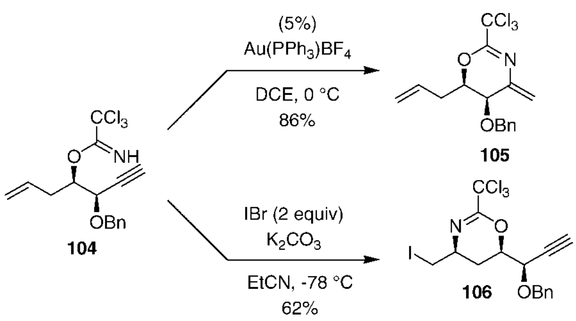
Scheme 62



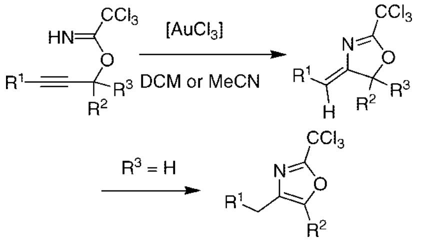
Scheme 63



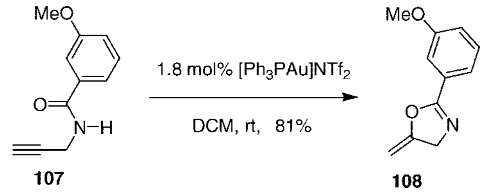
Scheme 64



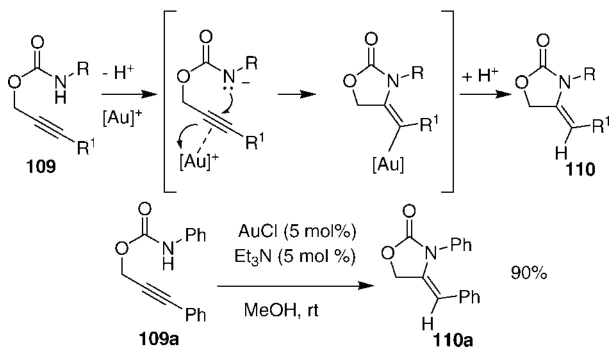
Scheme 65



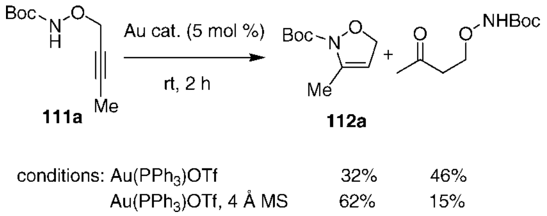
Scheme 66



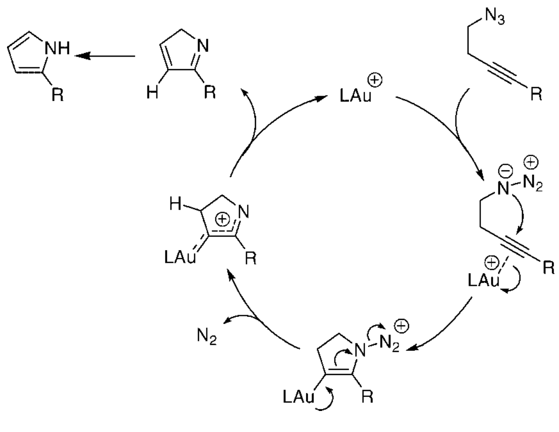
Scheme 67



Scheme 68



Scheme 69

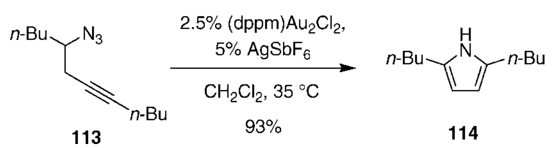


The (*p*-methoxyphenyl)methyl sulfide, **121a**, was converted into the corresponding benzothiophene, **122a**, in 98% yield in the presence of 2 mol % of AuCl (Scheme 75).

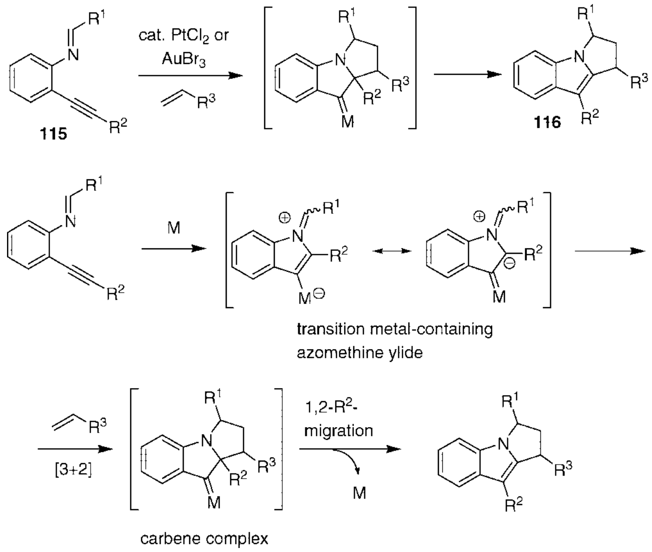
A plausible mechanism for this gold-catalyzed reaction is illustrated in Scheme 76. Gold(I) chloride is coordinated by the triple bond of substrate **121**. Nucleophilic attack of the sulfur atom of **123** at the alkynyl moiety gives the cyclized intermediate **124**. The catalytic cycle is completed by trapping of the vinyl−Au intermediate with the *R*-alkoxyalkyl, allyl, and benzyl groups, in an intramolecular fashion.

It was also recently reported that a vinyl−Au intermediate can be intramolecularly captured by silicon electrophiles, so-called silyldemetalation.[138] The gold-catalyzed cyclization of (*ortho*-alkynylphenylthio)silanes **126** produced the corresponding 3-silylbenzo[*b*]thiophenes **127** in good to excellent yields. The reaction proceeded under mild conditions without the formation of undesired byproducts, making this methodology useful for the synthesis of highly functionalized 3-silylbenzo[*b*]thiophenes in an environmentally benign manner (Scheme 77).

Scheme 70



Scheme 71



Propargylic sulfides and dithioacetals **128** are found to afford indene derivatives **129** through pentannulation of aromatic rings (Scheme 78).[139]

The reaction presumably involves Au carbene as the reactive intermediate (Scheme 79).

2.7. Hydroxylation Reactions of Allenes

Gold-catalyzed cyclization reactions of allenyl carbinols were investigated by Krause et al. Recently, novel furanomycin analogues **131** were synthesized as mixture of two diastereomers using the gold-catalyzed cyclization of α-hydroxyallenes **130** as the key step (Scheme 80).[140]

Compared to the traditional use of stoichiometric amounts of silver salts, gold catalysis is much more efficient for the cyclization of highly functionalized substrates. Hydroxy-3,4-dienoates **132a–b** were smoothly converted into the corresponding tri- and tetrasubstituted 2,5- dihydrofurans **133a–b** by simple treatment with HCl gas in chloroform or more conveniently by using acidic Amberlyst 15 resin in refluxing dichloromethane.[141] The transformation proceeds under perfect chirality transfer, furnishing the desired heterocycles in good yields and diateroselectivities of up to 90%. However, acid-labile substrates (i.e., silylated hydroxyallenes) or those that would readily undergo elimination reactions to the corresponding vinyl allenes are incompatible with this method. In addition, bases, or fluoride,[142] transition metals such as Pd(II)[143] or Ag(I)[144] have been used for this purpose. The method of choice, however, is the use of homogeneous gold catalysts because this combines a high reactivity and excellent stereoselectivity with a tolerance to many functional groups. Indeed, under the presence of a catalytic amounts of $AuCl_3$ (5−10%), the ester-substituted 2,5- dihydrofurans **133a−d** have been obtained with good to excellent yields in dry dichloromethane at rt (Scheme 81).

As in the acid-induced cyclization, the reaction not only proceeded under complete chirality transfer but also proved to be of wide scope with regard to the substitution pattern of the allenic entity, furnishing both, tri- and tetrasubstituted 2,5-dihydrofurans. Whereas the cycloisomerization of phenyl-substituted α-hydroxyallene **134** to 2,5-dihydrofuran **135** catalyzed by gold(I) or gold(III) chloride takes place with considerable epimerization, high levels of axis-to-center chirality transfer can be reached in the presence of additives (e.g., 2,2′-bipyridine), by using a moderately coordinating solvent (e.g., THF) or by lowering the reaction temperature (Scheme 82).

The increased stability and selectivity of the catalysts thus formed allows their application to the cycloisomerization of various functionalized α- and *β*-hydroxyallenes, as well as a decrease of the catalyst loading to 0.1%.[145] This mild and efficient method has been applied to the synthesis of natural product derivatives. One of the synthetic approach to the totals synthesis of citreoviridin and its metabolite citreoviral, which is far less toxic, relied on the heterogeneous Ag(I) cyclization of hydroxyallene **136** to the citreoviral precursor **137** (Scheme 83).[146] There, almost stoichiometric amounts of silver nitrate were required to achieve a good yield of product **137**. The TBS−ether α-hydroxyallene **136** was converted into the corresponding dihydrofuran derivative upon treatment with only 5 mol % of $AuCl_3$ in dichloromethane (80% yield). Compared to Ag(I)-promoted cyclization, gold(III)-catalysis proved to be advantageous not only for economical and ecological reasons but also in terms of reactivity. Thus, complete conversion of **136** was achieved in 3 h at room temperature, furnishing **137** after removal of the catalyst as a 60:40 mixture of diastereomers in 80% yield. No aqueous workup is required: the desired heterocycles are obtained spectroscopically pure just after evaporation of the solvent, followed by short flash column chromatography to remove the metal catalyst.[147]

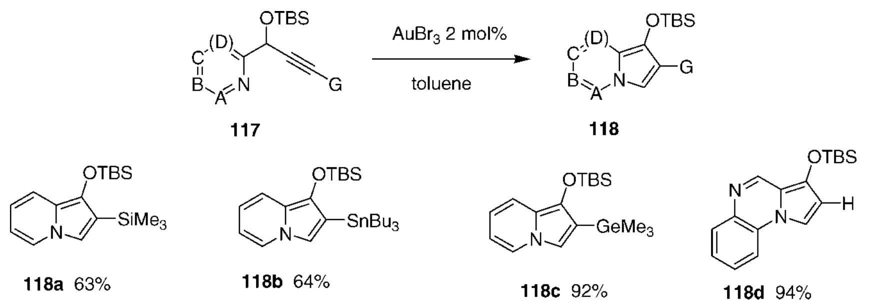
More recently, the first enantioselective total syntheses of the *β*-carboline alkaloids (−)-isochrysotricine **138** and (−)-isocyclocapitelline **139** have been accomplished (Scheme 84).[148] This synthesis clearly demonstrates that homogeneous gold catalysis is a perfect tool for the stereoselective construction of complex natural products.

The cycloisomerization of *β*-hydroxyallenes **140** led to dihydropyrans **141** (Scheme 85).[149] Both gold(I) and gold(III) were found to be competent precatalysts and afforded the 6-endo-cyclization product **141** with ∼60% yield. No trace of the 5-exo-isomer could be detected. Interestingly, the yield was hardly affected by the solvent and the presence of silver salts, which leads to the formation of cationic gold species. Further experiments with cationic gold catalysts in noncoordinating solvents made it possible to decrease the reaction time considerably. The method was extended to the *β*-aminoallene, which afforded tetrahydropyridine in good yield as well.

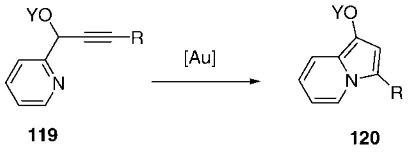
The gold(I)-catalyzed 6-endo-cycloisomerization of *β*-hydroxyallenes **142** provides a mild and efficient access to chiral functionalized dihydropyrans **143**, which were obtained at room temperature in good chemical yields with axis-to-center chirality transfer (Scheme 86).

Chiral *γ*-substituted allenamides **144** have been shown to undergo efficient gold-catalyzed cyclization to highly functionalized dihydrofurans **145** (Scheme 87).[150] Reactions proceed rapidly and without loss of stereochemistry in contrast with the Brønsted acid-catalyzed and TBAF-mediated cyclization which displayed no or poor diastereoselectivity.[151]

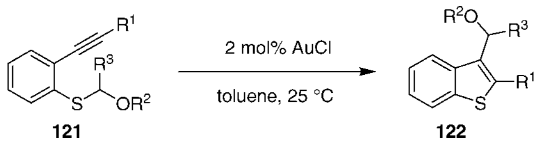
Scheme 72



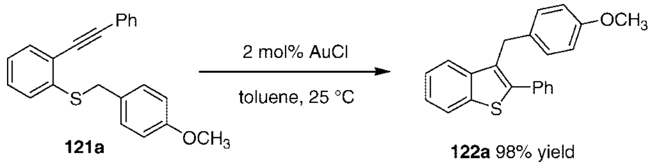
Scheme 73



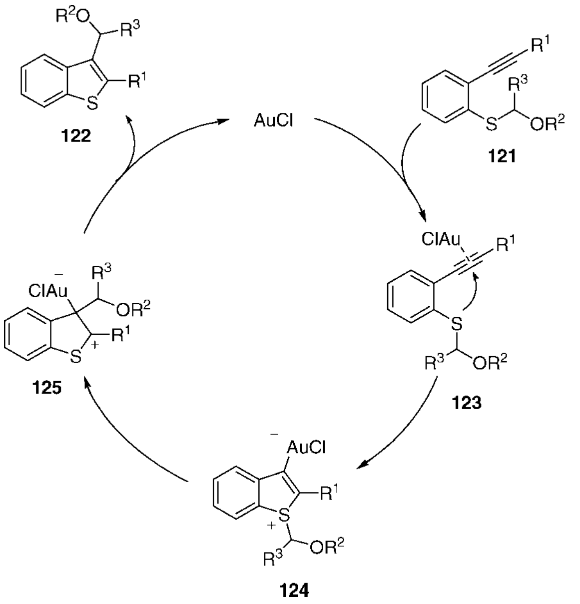
Scheme 74



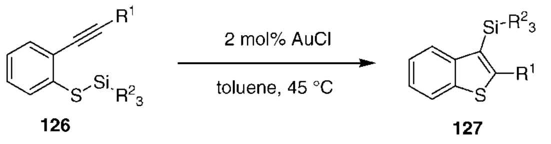
Scheme 75



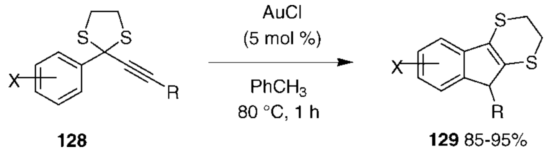
Scheme 76



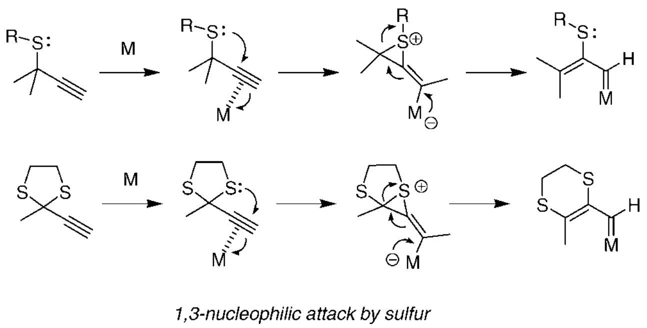
Scheme 77



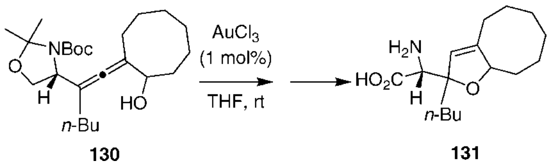
Scheme 78



Scheme 79



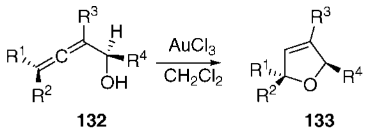
Scheme 80



γ-Hydroxy and δ-hydroxy allenes underwent Au-catalyzed intramolecular hydroalkoxylation within minutes at room temperature to form the corresponding oxygen heterocycles in good yield with high exo-selectivity.[152] For example, reaction of the γ-hydroxyallene **146** with a catalytic 1:1 mixture of [Au{P(*t*-Bu)$_2$(o-biphenyl)}Cl] **147** and AgOTs (Ts = toluene-*p*-sulfonyl) at room temperature for three minutes gave the 2-vinyltetrahydrofuran **148** in 91% yield (Scheme 88).

The rate, efficiency, and stereoselectivity of this hydroalkoxylation pointed to the feasibility of an analogous enantioselective protocol. Au$_2$ complexes of the form [Au2(P−P)Cl$_2$] (P−P = 2,2′-bis(diarylphosphino)-biphenyl), activated by AgOTs, as precatalysts, have been targeted for the enantioselective hydroalkoxylation of allenes. Optimization studies identified (*S*)-**149** as an effective supporting ligand for enantioselective hydroalkoxylation (Scheme 89). Employment of AgOTs as a cocatalyst was fortuitous as the yields and enantioselectivities were significantly higher than when a range of common silver salts were used. Also noteworthy was that nonpolar solvents provided considerably higher enantioselectivities than polar solvent. Toluene emerged as an attractive solvent because of its low melting point and the high rate of hydroalkoxylation in toluene.[153] The absolute

Scheme 81



132 **133**

	R^1	R^2	R^3	R^4	
132a	*t*-But	Me	H	CO_2Et	**133a** (74%)
132b	*t*-But	Me	Me	CO_2Et	**133b** (94%)
132c	*t*-But	H	Me	CH_2OTBS	**133c** (95%)
132d	*t*-But	Me	Me	CH_2OMe	**133d** (90%)

configuration of the catalyst (*S*) determines the configuration of the sp^3 stereocenter of the product (*R*).

2.8. Hydroamination Reactions of Allenes

Intramolecular cyclization of allenes with tethered amines, in the presence of a transition metal catalyst represents the most common route for generating nitrogen-containing heterocycles. Silver and mercury salts have been used for this purpose.[154] However, the Lewis acidity of the former catalyst and toxicity of the latter catalyst restrict their use in the hydroamination. An alternative strategy involves the use of organolanthanides[155] and titanium,[156] as well as group 4 metal-bis(sulfonamido) complexes.[157] Palladium-catalyzed reactions of cyclization of aminoallenes occurred under acidic conditions.[158] The use of a carboxylic acid as an additive and high reaction temperature (70 °C) were the drawbacks of the palladium-catalyzed hydroamination.[159] Moreover, although many catalysts such as $Pd(OAc)_2$, $PdCl_2$, $[Pd(PPh_3)_4]$, and $[Pd_2(dba)_3]\cdot CHCl_3$ failed to give the desired cyclized products, exposure of 4-(1′-methylallenyl)-2-azetidinone **150** to 5 mol % $AuCl_3$ in CH_2Cl_2produced the bicyclic *β*-lactam product **151** in 65% yield (Scheme 90).[160]

Yamamoto and co-workers reported results concerning Au(I)- and Au(III)-catalyzed room-temperature intramolecular hydroamination of allenes leading to pyrrolidines and piperidines.[161] Wherein the amine was not protected by any protecting group, did not give any desired product; a complex mixture was obtained. The scope and synthetic utility of the gold-catalyzed process has been enhanced dramatically by chirality transfer from the starting aminoallenes to the products (Scheme 91).

Indeed, treatment of enantiomerically pure aminoallene **152** with 1 mol % AuCl in THF at rt gave pyrrolidine **153** in excellent yield with 94% ee (Scheme 92).

The gold-catalyzed cycloisomerization of various α-aminoallenes **154** afforded the corresponding 3-pyrrolines **155** in good to high chemical yields and, if the amino group is unprotected, with complete axis-to-center chirality transfer (Scheme 93).[162] The low reactivity of the intramolecular hydroamination of unprotected α-aminoallenes with $AuCl_3$ was improved by use of gold(I) halides as the precatalyst. Mechanistic studies suggest that a gold(I) compound (formed by oxidation of the aminoallene) is the catalytically active species even if the reaction is started with a gold(III) precatalyst. Diminished levels of chirality transfer were observed in cases of N-protected substrates, which may be the result of partial epimerization of the allene in the presence of the gold precatalyst.

The system optimized for the enantioselective hydroalkoxylation of allenes was targeted to the enantioselective hydroamination of *N*-allenyl carbamates.[163] Chiral dinuclear gold(I)-phosphine complexes **156** could act as efficient catalysts for the asymmetric hydroamination (Scheme 94).

Treatment of the *N*-4,5-hexadienyl carbamate **157** with a catalytic 1:2 mixture of [(S)-**149**]$Au_2Cl_2$and $AgClO_4$ in *m*-xylene at −40 °C for 24 h led to isolation of 2-vinylpyrrolidine **158** in 97% yield with 81% ee (Scheme 95). Gold(I)-catalyzed enantioselective hydroamination was effective for a number of carbamate groups and tolerated terminal disubstitutution of the allenyl moiety.

Toste and co-workers highlighted the dramatic amplification of the enantiomeric excess observed when benzoate counterions were employed in the intramolecular hydroamination of tosyl allenes.[164] This discovery resulted in the development of phosphinegold(I)-bis-*p*-nitrobenzoate complexes as catalysts for enantioselective formation of vinyl-substituted pyrrolidines and piperidines. The intramolecular hydoammination of **159** led to the formation of the vinyl disubstituted pyrrolidine **161** in 88% yield and 98% ee by using 3 mol % of (*R*)-xylyl-BINAP-$(AuOPNB)_2$ **160** an isolable, bench-stable complex as catalyst (Scheme 96). Importantly, a variety of BINAP and biaryl-based gold complexes were found to catalyze this transformation with good enantioselectivity.

Traditionally, transition metal-catalyzed enantioselective transformations rely on chiral ligands tightly bound to the metal to induce asymmetric product distributions. Very surprisingly, high enantioselectivities can be conferred by a chiral counterion in gold-catalyzed hydroalkoxylation and hydroamination of allenes.[165] These transformation catalyzed by cationic gold(I)-generated products in 90 to 99% enantiomeric excess with the use of chiral binaphtol-derived phosphate anions. Furthermore, the chiral counterion can be combined additively with chiral ligands to enable an asymmetric transformation that cannot be achieved by either method alone.[166]

An important aspect of hydroamination is the relative difficulty in achieving intermolecular hydroamination as compared to the intramolecular version. However, only few examples are known for the intermolecular hydroamination of allenes. Group 4 metal-catalyzed[167] and palladium-catalyzed[168] hydroamination of allenes with aryl amines have been reported. The intermolecular hydroamination of allenes **162** with aniline takes place with $AuBr_3$ at ambient temperature in THF to give the corresponding allylic amines **163** in good to high yields (Scheme 97).[169]

Furthermore, the axial chirality of allenes **164** can be transferred with very high ee values to the products **165** (Scheme 98).

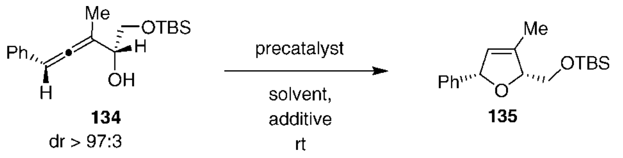
The intermolecular hydroamination with aliphatic amines is more difficult. Yamamoto and Nishina succeeded in running the gold(I)-catalyzed intermolecular hydroamination with an aliphatic amine and found that the control of steric environment around gold center by using appropriate phosphine ligands is a key for making it feasible to carry out such aliphatic hydroamination (Scheme 99).[170]

2.9. Hydrothiolation of Allenes

Various gold precatalysts, such as AuCl, AuI, $AuCl_3$, or $AuBr_3$, induced the stereoselective cycloisomerization of α-thioallenes **166** to furnish the 2,5- dihydrothiophene **167** in good to excellent yields (Scheme 100).[171] Conversely, copper or silver precatalysts afforded no cyclization products.

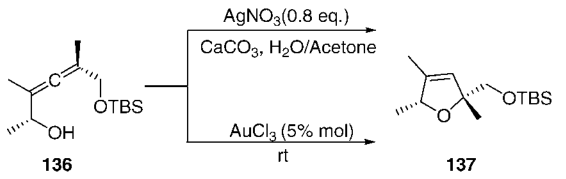
Interestingly, the reaction time can be decreased dramatically by changing the halide anion in the order Cl > Br >

Scheme 82

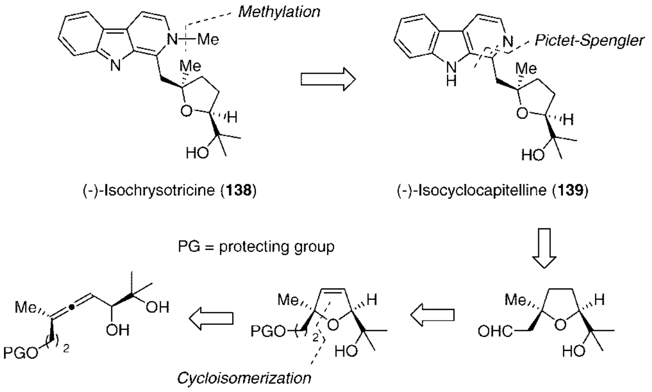


Precatalyst (mol%)	Solvent	Additive (mol%)	Time (h)	Yield (%)	*cis:trans*
$AuCl_3$ (2.5)	CH_2Cl_2	2,2'-Bipyridine	1	70	> 97:3

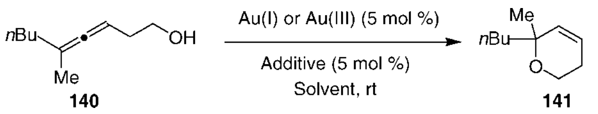
Scheme 83



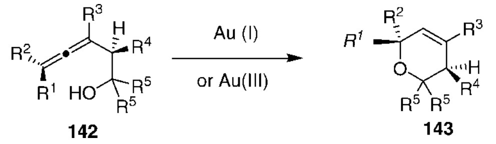
Scheme 84



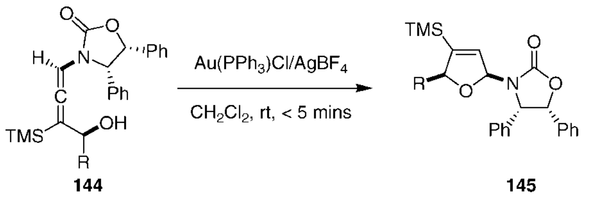
Scheme 85



Scheme 86

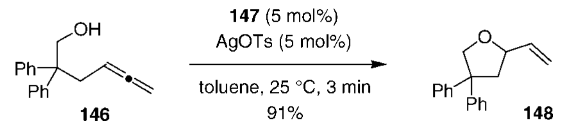


Scheme 87

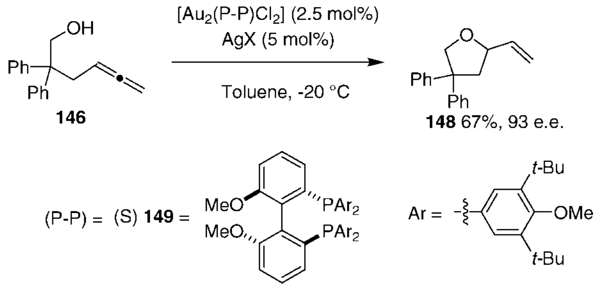


5 examples, 78-87%

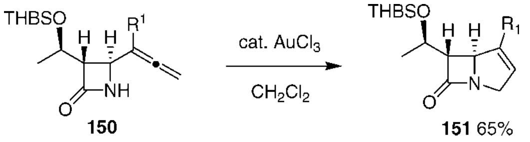
Scheme 88



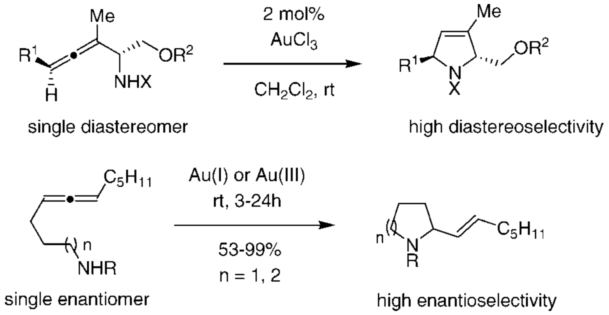
Scheme 89



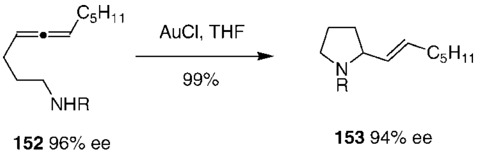
Scheme 90



Scheme 91

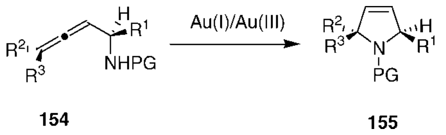


Scheme 92

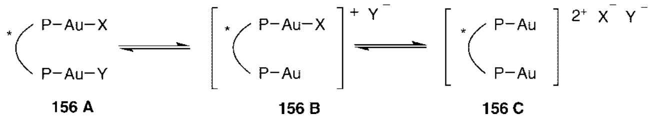


I. By using the highly active gold(I) iodide, the catalyst loading could be reduced to 1 mol%. Not surprisingly, the less Lewis acidic [Ph_3PAuCl] does not catalyze the cycloisomerization. The use of $AuCl_3$ or $AuBr_3$ led to the formation of the disulfide as side product. A plausible mechanistic model of the gold-catalyzed cycloisomerization of α-thioallenes to 2,5-dihydrothiophenes is shown in Scheme 101. Coordination of the carbophilic gold catalyst to the "terminal" allenic double bond (intermediate **168**) is required for an intramolecular nucleophilic attack of the thiol via an S_N2-type transition state to afford the zwitterionic species **170** which upon protodemetalation is transformed into the heterocyclic product with complete axis-to-center chirality transfer. Compared to the other heteroatom-substituted allenes, however, coordination of the gold catalyst to the sulfur atom of the α-thioallenes (complex **169**) is probably more pronounced than its coordination to other heteroatoms, causing a lower reactivity. The observation of a disulfide as a side product if a gold(III) salt is used as the precatalyst,

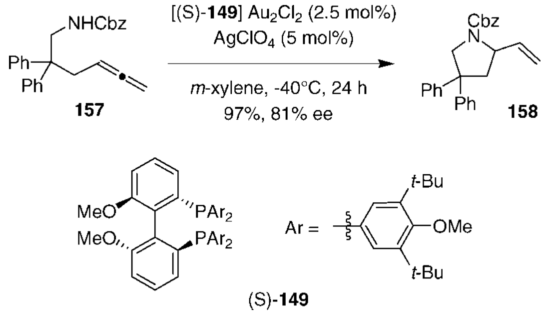
Scheme 93



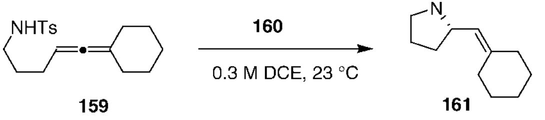
Scheme 94



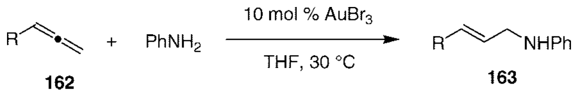
Scheme 95



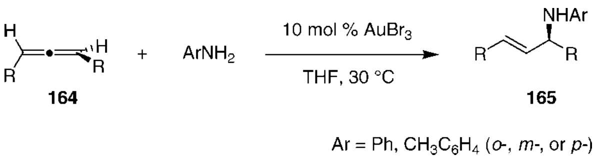
Scheme 96



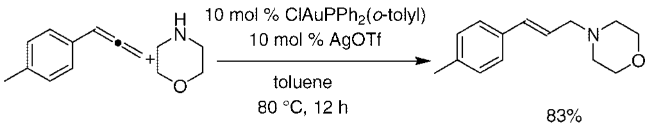
Scheme 97



Scheme 98



Scheme 99

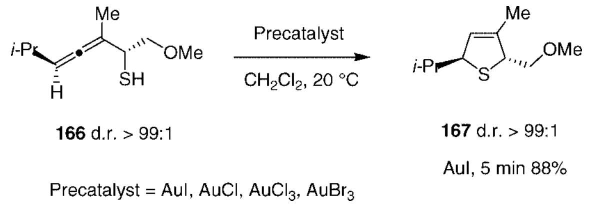


may indicate that a gold(I) compound is the catalytically active species in all cases.

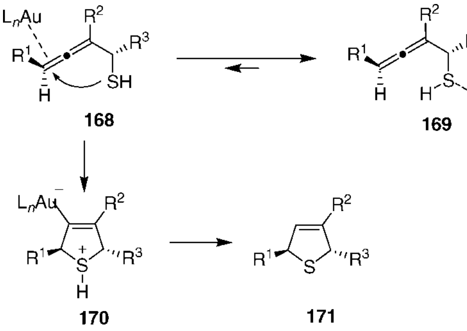
2.10. Hydroalxoxylation of Alkenes and 1,3-Dienes

Mild, metal-catalyzed additions of N−H and O−H bonds across olefins have been sought for decades, and efforts to develop such processes have intensified in recent years. Triflic acid and sulfuric acid-catalyzed intramolecular additions of the N−H bond of sulfonamides, carbamates, acetamides, and benzamides across the C=C double bond of alkenes have been reported.[17] Alternatively, simple olefins can be activated by gold, even if they are surely less reactive than alkynes. The first important contribution in this field was published by He and Yang.[172] Intermolecular additions of phenols and carboxylic acids to alkenes can be catalyzed by $Ph_3PAuOTf$ under relatively mild conditions. The carbon−heteroatom bonds through activation of inert olefins have been traditionally mediated by acids or stoichiometic amounts of toxic reagents.[173] The reaction mechanism is proposed in Scheme 102.

Scheme 100



Scheme 101



Cationic gold(I) binds and activates alkene for a nucleophilic addition by the phenols or carboxylic acids, a reaction similar to the Wacker process catalyzed by palladium(II).[174] A subsequent proton-transfer step affords the final product and regenerates gold(I) catalyst. The gold catalyst also promotes migration of double bonds, which gives rise to formation of small amounts of side products for some substrates. The reaction is simple and runs under relatively mild conditions. Reactions were conducted with 1 mmol of nucleophiles, 4 mmol of olefins, and 2 mol % (for phenols) or 5 mol % (for carboxylic acids) of $Ph_3PAuCl/AgOTf$ in 2 mL of toluene at 85 °C to give in good yield the Markovnikov product **175**. Different solvents were screened, and toluene was found to be the best solvent for this reaction.

The same catalytic system was used to prepare dihydrobenzofurans **177** from aryl allyl ethers **176** through an intramolecular domino process (Scheme 103).[175]

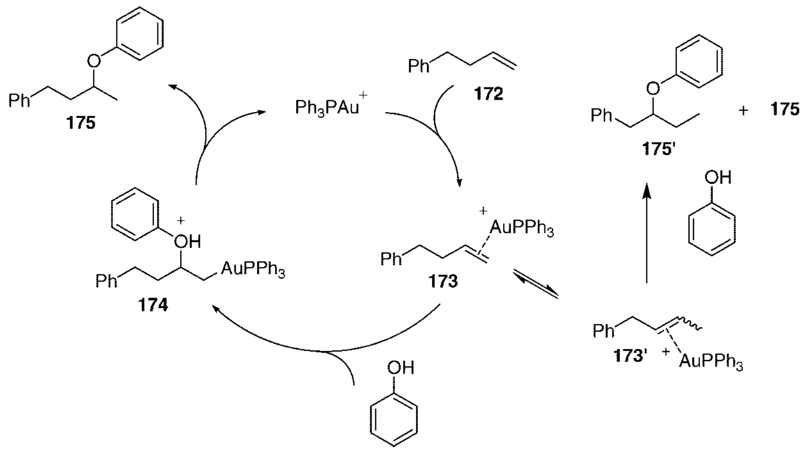
The reaction appears to proceed by a Claisen rearrangement, followed by addition of the resulting phenol to the allyl group. The authors gave the experimental evidence that cationic gold is capable of mediating both reaction steps, although the rearrangement is the rate-limiting step. On the other hands, other experiments demonstrate that the rearrangement step is faster in the presence of the more oxophilic gold(III) (Scheme 104).

Li and co-workers extended this principle to 1,3-dienes and found an interesting atom-economical annulation of phenols **178** to give benzofuran derivatives **179** (Scheme 105).[176]

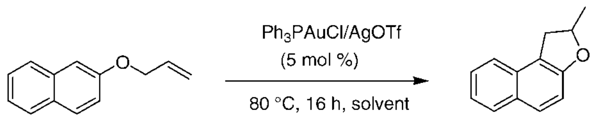
The reaction involves a sequential double addition of a carbon and an oxygen nucleophile to the diene. Interestingly, gold(III) gave best results whereas cationic gold failed.

The effective addition of alcohols to alkenes can also be catalyzed by Au(III) and carried out under mild conditions

Scheme 102



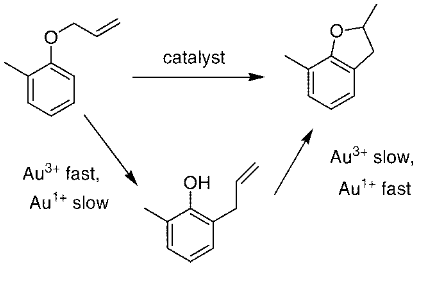
Scheme 103



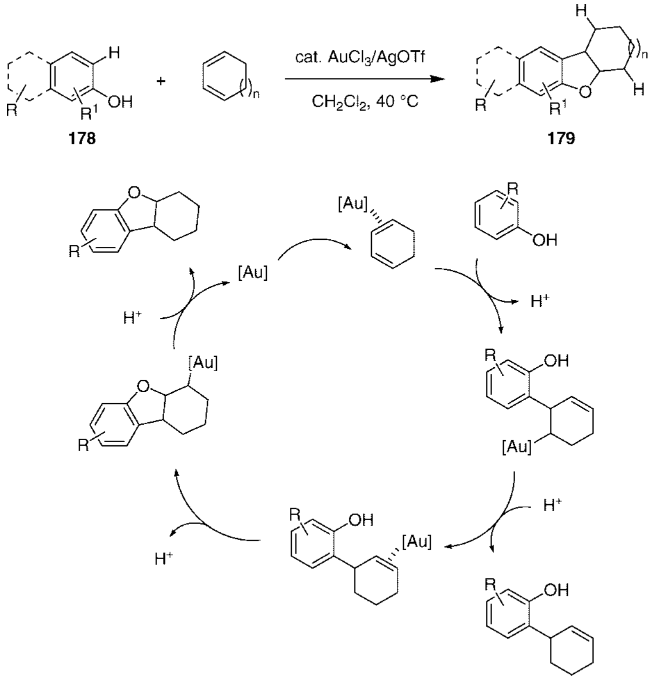
176

177 95%

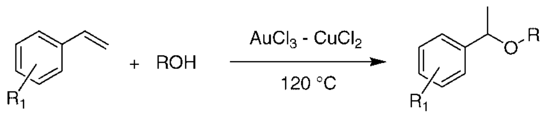
Scheme 104



Scheme 105



Scheme 106



R = Me, Et, Pr, Butyl, etc.
R_1 = H, Me, Cl

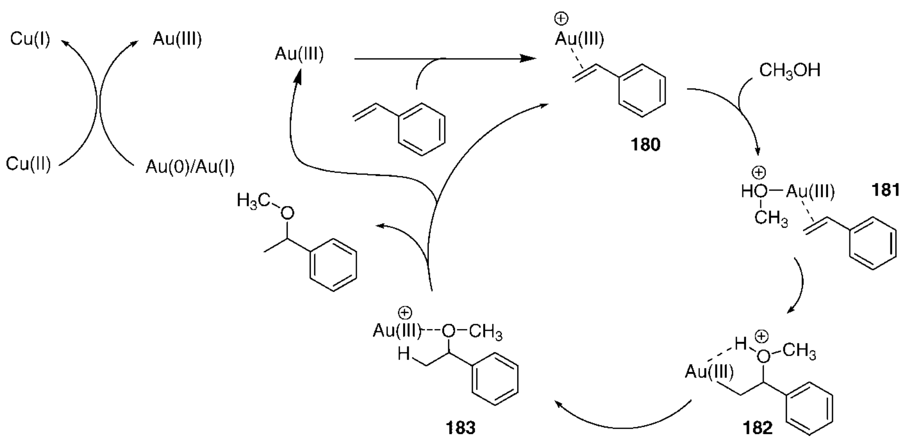
with catalytic amounts of $CuCl_2$, which significantly stabilize the cationic Au(III).[177] Of course, related acid-catalyzed additions of alcohols to alkenes are classic reactions in organic chemistry.[178] The stabilizing effect was proven through the observation that $AuCl_3$ (0.1 mmol) in 1.0 mL of methanol at 120 °C starts to form metallic particles after 2 min, while in the presence of $CuCl_2$ (0.2 mmol), no metallic particles were observed in one hour. The $AuCl_3-CuCl_2$ catalytic system has been applied to the addition of various alcohols to alkenes (Scheme 106). It is shown that the catalyst works very well for primary alcohols with styrene conversions in the order of 95% and the selectivity for the ether of 85%. Secondary alcohols react more slowly than primary alcohols, while tertiary alcohols have very low reactivity. Interestingly, addition of ethylene glycol is also effective. The alcohols can also be added to other alkenes, following Markovnikov's rule.

In the reaction mechanism for the addition of alcohols to alkenes over Au(III)$-CuCl_2$, Au(III) acts as a Lewis acid that activates the alkene to form the corresponding gold complex **180**, which is then attacked by the alcohol to form the intermediate complex **181**(Scheme 107). Both **181** and the transition state **182** would be sterically quite crowded, and this could be the reason why secondary alcohols react more slowly than primary alcohols while tertiary alcohols fail in this reaction. A rearrangement of **182** to **183** affords the final product and regenerates the Au(III) catalyst. However, there is a parallel process in which Au(III) is reduced into the less-active Au(I) and then into the nonactive Au(0). This makes the reaction stop at low levels of conversion, unless the reduction process is slowed down by the redox cycle in the presence of $CuCl_2$.

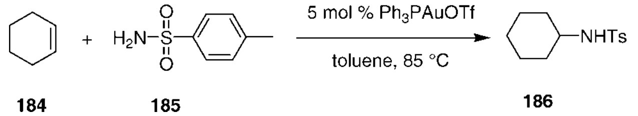
2.11. Hydroamination of Alkenes and 1,3-Dienes

The hydroamination reaction of alkenes have been traditionally carried out in the presence of alkali metals, lanthanides, and group 4 complexes.[105b] The proton-catalyzed addition of amines to alkenes by using $PhNH_3B(C_6H_5)_4 \cdot Et_2O$ as the promoter has been described.[179] The hydroamination reaction using a palladium[180] and rhodium complexes has been explored.[181] More recently, catalysis by early transition metals have been investigated.[182] Lewis acids could also

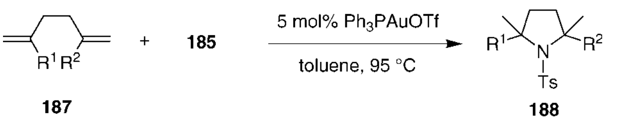
Scheme 107



Scheme 108



Scheme 109



R^1 = H, R^2 = H 64% (*cis/trans*:37/63)
R^1 = H, R^2 = Me 90%
R^1 = Me, R^2 = Me 80%

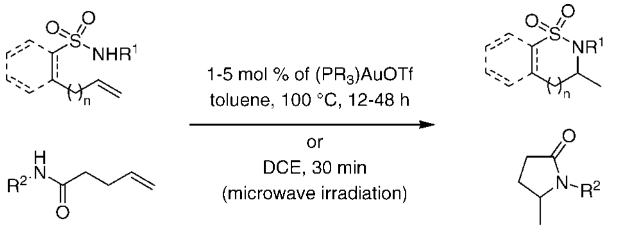
serve as competent catalysts.[183] Catalysis by late transition metals has been also explored,[184] and gold catalysts can provide alternative procedures for olefin hydroamination. He and Che described a very interesting inter- and intramolecular gold(I) hydroamination reaction. They tested reactions between cyclohexene **184** and various nitrogen nucleophiles. *N*-cyclohexyl-*p*-toluenesulfonamide **186** was prepared in 90% isolated yield by reacting *p*-toluenesulfonamide (TsNH$_2$) **185** with 4 equiv of **184** in toluene with a catalytic amount (5 mol %) of Ph$_3$PAuOTf (generated by mixing equal equivalents of Ph$_3$PAuCl and AgOTf) at 85 °C for 15 h (Scheme 108).[185]

Other Lewis acids, such as Zn(OTf)$_2$ and Cu(OTf)$_2$, could not catalyze the same reaction, and Sc(OTf)$_3$ gave less than 20% of the addition product under the same conditions. The hydroamination of 1,5-dienes **187** with TsNH$_2$ **185** produced pyrrolidines **188** in an "one-pot" operation (Scheme 109). The first intermolecular hydroamination of a 1,5-diene by **185** could be followed by a second intramolecular hydroamination.

Rapid and reliable microwave applications resulted advantageous for gold(I)-catalyzed intra- and intermolecular hydroamination of unactivated alkenes and could provide a useful tool for high-throughput synthesis (Scheme 110).[186] The use of microwave radiation as a heat source allows a convenient access to the temperature needed to allow completion of the reaction in a much shorter time than that required underconventional thermal conditions.

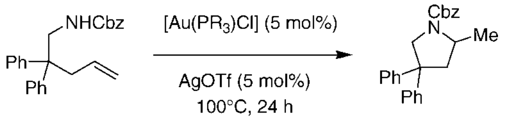
Electron-rich phosphines such as P(*t*-Bu)$_2$-(*o*-biphenyl) were particularly effective supporting ligands for intramolecular hydroamination of unactivated olefins under milder conditions and with broader substrate scope than previously realized with late transition-metal catalyst systems (Scheme 111).[187]

Scheme 110



n = 0, 1, 2 R^1 = H, Et, *t*-Bu R^2 = Ar, PhCO, Ts

Scheme 111



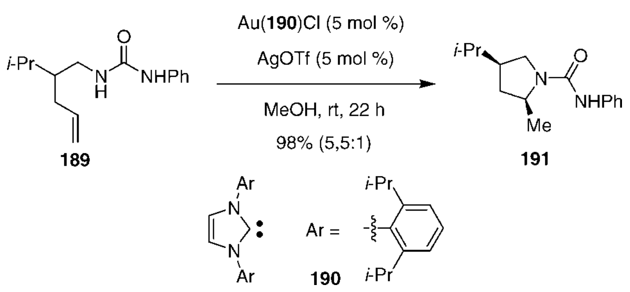
P(*t*-Bu)$_2$(o-biphenyl), dioxane, 98%
PPh$_3$, dioxane, 75%
P(*p*-CH$_3$O-C$_6$H$_4$)$_3$, dioxane, 70%
P(*p*-CF$_3$-C$_6$H$_4$)$_3$, dioxane, 23%

Treatment of an *N*-4-pentenyl or *N*-5-hexenyl urea with a catalytic 1:1 mixture of a gold(I) N,N-diaryl imidazol-2-ylidine complex and AgOTf at or near room temperature leads to intramolecular exo-hydroamination to form the corresponding nitrogen heterocycle in excellent yield.[188] As is the case with electron-rich phosphines, *N*-heterocyclic carbenes are strong σ-donors that form stable compounds with a diverse range of transition metals including gold(I).[189] In particular, the highly sterically hindered, commercially available 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine **190** resulted in an exceptionally active supporting ligand for the intramolecular hydroamination of *N*-alkenylureas **189**. The resulting nitrogen heterocycles **191** were formed in excellent yield with good regioselectivity and up to 5.5:1 diasteroselectivity (Scheme 112).

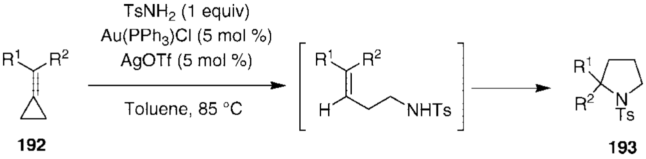
Reaction of methylenecyclopropanes **192** with sulfonamides produces the corresponding pyrrolidine derivatives **193** in moderate to good yields under the catalysis of Au(I) via a domino ring-opening ring-closing hydroamination process (Scheme 113).[190]

Interestingly, gold(I)-catalyzed intermolecular ring-opening of unactivated vinylcyclopropanes (VCPs) **194** with sulfonamides can allow the formation of useful derivatives of homoallylic amines **195** (Scheme 114).[191] Various metal catalysts, solvents and conditions were screened. The use of

Scheme 112



Scheme 113



10 mol% AuCl((PPh_3)/AgOTf and 3 equivs of **194** in toluene at 50 °C gave **195** in 73% isolated yield. The yield of **195** did not drastically change when using gold(I) complexes containing electron-rich or more sterically demanding phosphine ligands. On the other hand, catalysts with electron-deficient aryl phosphines led to the preferred formation of product **196**, isolated in moderate yields. Moreover, metal salts such as $AuCl_3$, AgOTf, and $Pd(OAc)_2$ were found to be catalytically inactive. The same reaction is also efficiently catalyzed by HOTf, thus making it more convenient for synthetic purposes.

$Ph_3PAuOTf$ catalysis has been extended to hydroamination of 1,3-dienes under mild conditions.[192a] A variety of carbamates and sulfonamides added to conjugated dienes to afford protected allylic amines in good to high yields (Scheme 115). The use of excess diene was not necessary.

Recently, the reaction mechanism of the gold(I)-phosphine-catalyzed hydroamination of 1,3-dienes was studied by means of density functional methods combined with polarizable continuum models. It was found that the most favorable series of reaction steps include the ligand substitution reaction in the catalytically active $Ph_3PAuOTf$ species between the triflate and the 1,3-diene. Subsequent nucleophile attack on the *N*-nucleophile on the activate double bond is followed by proton transfer from the NH_2 group to the unsaturated carbon atom. The role of the triflate counteranion acting as a proton shuttle is consistent with experimental findings.[192b]

2.12. Hydrothiolation of Conjugated Olefins

The addition of thiols to conjugated dienes can be simply achieved by radical initiators or by Brønsted acid catalysis.[193] However, radical-based mechanisms result in competing telomerization when using alkyl-substituted thiols, and strong Brønsted acids are incompatible with many synthetically useful functional groups. Furthermore, with styrene substrates, radical processes produce anti-Markovnikov addition of the thiol, while acid-based catalysts produce the corresponding Markovnikov addition products. Earlier attempts to demonstrate Markovnikov addition with Lewis acid catalysts, such as titanium(IV) chloride and aluminum(III) chloride, have required stoichiometric amounts of the metal.[194] Thiol additions to conjugated olefins can be catalyzed by Ph_3PAuBF_4 with excellent yields at room temperature (Scheme 116).[195]

A variety of functionalized thiols, with both electron-donating and -withdrawing substituents, are compatible with this system. Hydrothiolations of 1,3-cyclohexadiene were also achieved in similar yields at 50 °C. Like most reported gold-catalyzed processes, the hydrothiolation reaction required noncoordinating counteranions. Many solvents were screened, and only chlorinated solvents afforded products. Dichloromethane and chloroform were the best for the reaction.

3. Activation of Carbonyl/Imine Groups and Alcohols

The reasons of the recent growing popularity of gold catalysts used as Lewis acids in various catalytic transformations have been recently highlighted by Yamamoto.[196] Classic Lewis acids, such as BCl_3, and $AlCl_3$, are known to make strong σ-complexes with carbonyl and imine groups[197] that make them versatile catalysts of the Friedel−Crafts and other electrophilic reactions.[198] On the other hand, the salts of transition metals can operate as bifunctional Lewis acids activating either (or both) carbon−carbon multiple bonds via π-binding or make the σ-complexes with heteroatoms. Heats of formation for the generation of complexes between unsaturated compounds with representative metal chlorides[199] have been computed with the aim to classify various Lewis acids by their relative ability for making π- and σ-complexes with appropriate substrates. The values of the $\Delta H^{\text{carbonyl(imine)}}$ and $\Delta H^{\text{acetylene(alkene)}}$ can represent an useful tool for the deliberate choice of catalysts for the desired transformations, especially in the cases when bi- or polyfunctional substrates are involved. Comparing the ratios of the heats of formation for the Lewis acids containing the same metal in different oxidation state (CuCl and $CuCl_2$, AuCl and $AuCl_3$), one can conclude that the lower oxidation state of the catalyst increases the relative strength of coordination to the carbon−carbon multiple bonds. Moreover, the relative affinity to the carbon multiple bonds increase with decreasing nucleophilicity of the anion.

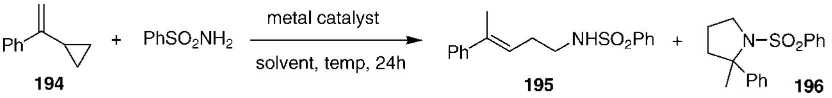
3.1. Condensation Reactions

Recent state-of-art research in organic chemistry requires the design of highly selective transformations. In other words, only desired reaction(s) must take place when the substrate is treated with the reagent, even if the structure of the substrate suggests numerous possibilities for reactivity. Gold catalysts often provide this kind of selectivity. Arcadi and co-workers developed an useful strategy to obtain functionalized pyrroles through a gold-catalyzed sequential amination/annulation/protonolysis/isomerization reaction (Scheme 117).[200]

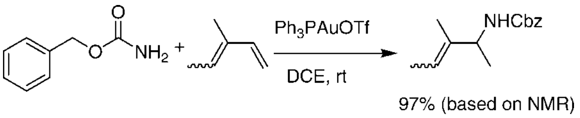
The formation of the pyrrole derivative **198** was suggested to proceed through the formation of the enaminone derivative **199**. The regioselective cycloamination of the enaminone **199** by the anti-addition of nitrogen and gold moieties in 5-exo-dig manner to the acetylenic bond gave a vinylaurate species **200**. The following protonolysis of C_{sp^2}−Au bond and isomerization reactions afford the pyrrole **198** (Scheme 118).

Although the interaction to acetylenic bond is one of the interesting feature of gold(III) catalysis, in the case above $NaAuCl_4$ had the further specific quality of accelerating the condensation of ketones with primary amines. Indeed, the competitive formation of 5-methylene-4,5-dihydrofuran derivatives through tandem intramolecular oxymetalation/ pro-

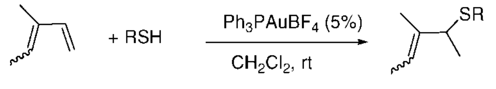
Scheme 114



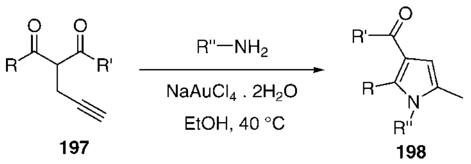
Scheme 115



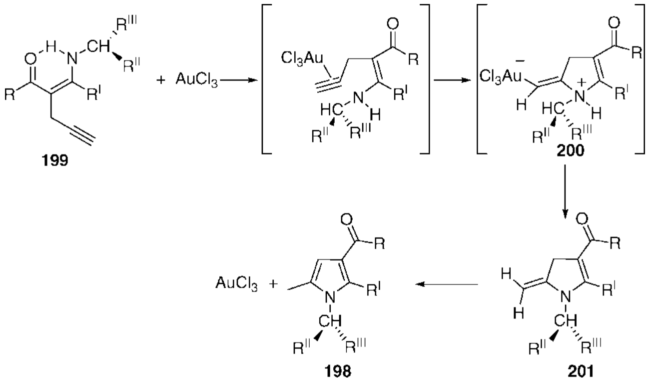
Scheme 116



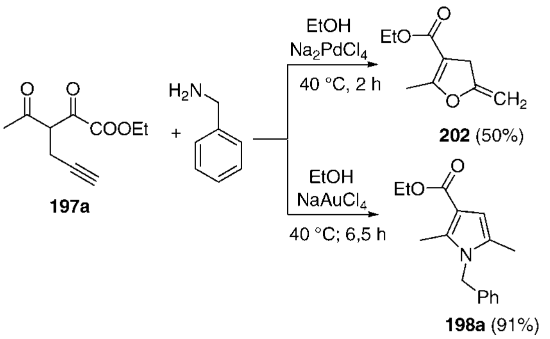
Scheme 117



Scheme 118



Scheme 119



tonolysis reactions[201] prevailed over the formation of the pyrrole nucleus under the presence of a palladium catatalyst. The reaction of ethyl 2-acetyl-4-pentynoate **197a**, that is, led chemoselectively to the formation of 2-methyl-3-acetyl-5-methylene-4,5-dihydrofuran **202** in the presence of Na_2PdCl_4 as catalyst. By contrast the formation of the pyrrole **198a** was observed by using $NaAuCl_4$ instead of Na_2PdCl_4 as catalyst (Scheme 119).

The above results clearly point out that the condensation reaction of **197** with primary amines must be faster than the oxymetalation reaction to allow the chemoselective formation of the pyrrole nucleus. On the basis of the assumption that the stereogenic center in the starting amine is not affected during this transformation, subsequent extension of the procedure to enantiomerically pure amines, *β*-amino alcohols and α-aminoesters led to the preparation of the target 1,2,5-trisubstituted pyrroles **198b**−**f** in homochiral form (Scheme 120).[202]

More recently a similar path to pyrroles was reported by the group of Dake.[203] The authors said that either silver or gold catalysts efficiently promote this transformation, but gold(I) precatalyst showed a greater thermal stability, whereas silver salt increased the speed of the reaction and gave slightly better yields (Scheme 121).

Gold catalyst can also simultaneously catalyze the nucleophilic attack of the amino group of the propargylamine to the carbonyl carbon through the formation of a complex with the C═O group and promote the nucleophilic attack of the enamine intermediate over a carbon−carbon triple bond by forming a complex with the alkyne group according to the following scheme 122.[204]

Indeed, the reaction of of dialkyl acyclic/cyclic ketones, methyl, aryl/heteroaryl ketones, and aldehydes bearing α-hydrogens with propargylamine gives rise to pyridines **203** through a gold-catalyzed sequential amination/6-endo-dig annulation/ aromatization reaction (Scheme 123). Gold(III) catalysts were very effective. Copper salts were also effective catalysts when reactive ketones are used. Conversely, $ZnCl_2$, $AlCl_3$, $TiCl_4$, and other Lewis acids showed low activity. The synthetic approach was successfully extended to the synthesis of steroidal derivatives with fused pyridine rings and polyannelated pyridines. Whereas linear polycyclic pyridines are regioselectively obtained by the gold-catalyzed condensation reaction of polycyclic carbonyl compound, the angular polycyclic pyridines are obtained starting from the corresponding α,*β*-unsaturated derivatives. Selective amination of the unsaturated carbonyl groups was observed in polycyclic dicarbonyl compounds.

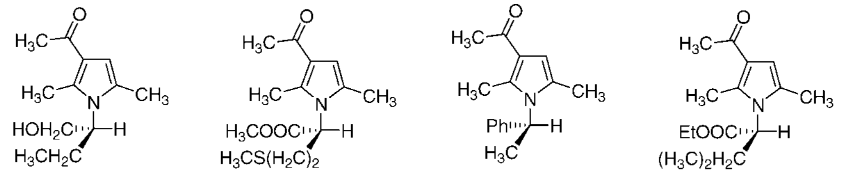
Polysubstituted quinolines have been readily prepared under milder conditions than in other previous reported methods through a gold(III)-catalyzed sequential condensation/annulation reaction of *o*-amino aromatic carbonyls and ketones containing active methylene groups (Scheme 124).[205] The Friedländer condensation is a two-step process including enamine formation and cyclodehydration. In its gold-catalyzed version, $NaAuCl_4$ catalyzes the first step.

In the course of a medicinal chemistry program directed at the synthesis of novel GABAB enhancers, the protocol of Arcadi[205] was applied to a wide range of 1,3-diones including *β*-keto-esters, *β*-diketones, *β*-keto-amides, and *β*-keto-sulfones to address various substitution patterns on the quinoline nucleus.[206] Exclusive regioisomer formation has been observed in the gold-catalyzed Friedländer reaction with special 1,3-diketones (Scheme 125).

The gold-catalyzed amination was extended to the developmnent of a greener approach to the synthesis of *β*-enamino esters and enaminoketones **208** according to Scheme 126.[207]

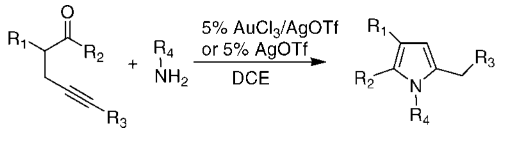
The procedure is quite general for a wide range of amines, such as aliphatic, cyclic, and aromatic amines, and ammonia. Results shown in Scheme 127 in comparison with those reported in the literature by traditional methodologies show

Scheme 120

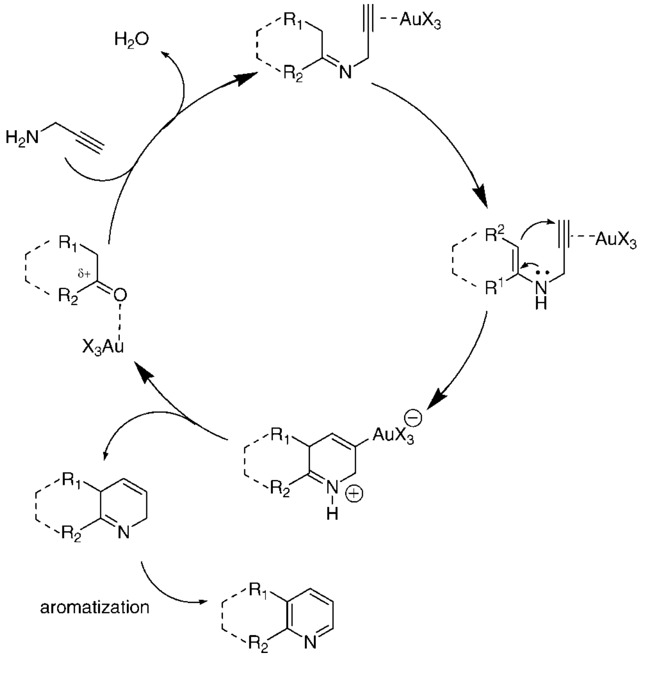


198b (86%, e.e. = 98%) **198c** (74%, e.e. = 99%) **198d** (96%, e.e. = 97%) **198f** (80%, e.e. = 98%)

Scheme 121



Scheme 122



that the gold-catalyzed condensation reaction of 1,3-dicarbonyls **206** and amines **207** to give **208** provides a remarkably viable alternative route for the synthesis of enaminones. All the reactions have been carried out at room temperature. It should be pointed out that in the reaction of aryl-alkyl-dicarbonyls with amines was observed the regioselective amination of the aliphatic carbonyl group (Scheme 127, **208b**). In addition when the 1,1,1-trifluoroacetylacetone and 1-(2-thenoyl)-3,3,3,-trifluoroacetone were allowed to react with amines only the enaminones derived from regioselective amination were observed (Scheme 127, **208d** and **208e**).

The effectiveness of gold(III) catalysis in the reaction of 1,3-dicarbonyls with N-, O-, S-, and P-nucleophiles has been also investigated. Moreover, gold(III) derivatives are efficient catalysts for the direct selective alkenylation reaction of indoles and pyrroles with 1,3-dicarbonyl compounds (Scheme 128).[208] $NaAuCl_4 \cdot 2H_2O$ (5 mol %) in acetonitrile afforded satisfactory results. $AuCl_3$ and $AuBr_3$ can also catalyze the reaction, but they gave the products in better yield in combination with silver(I) salts. The silver catalyst alone did not efficiently catalyze the alkenylation of indoles under the same conditions. Both gold(III) and silver(I) precatalysts have similar reactivity in the alkenylation reaction of pyrroles. Higher reactivity of silver salts was shown for the functionalization of furans.[209]

The method allows high functional group tolerance, regioselectivity, and scope under relatively mild conditions. The 3-alkenylindoles **210** can also be readily available through gold-catalyzed sequential cyclization/alkenylation reaction of 2-alkynylanilines **209** with 1,3-dicarbonyl compounds. This sequential reaction can be directed by increasing the reaction temperature (Scheme 129).

Electron-rich arenes condense efficiently with various carbonyl compounds under the influence of $AuCl_3$, thus opening up a practical route to triarylmethanes, which have important applications (Scheme 130). The mild conditions employed are especially noteworthy.[210] Various heterocyclic and aryl aldehydes, as well as aliphatic aldehydes, underwent the reaction smoothly. An electron-rich arene, 1,3,5-trimethoxybenzene, required the catalytic system $AuCl_3$/3AgOTf and a slightly elevated temperature (50 °C) to condense effectively with benzaldehyde. However, with a more activated electrophile (4-nitro benzaldehyde), the reaction took place at room temperature to afford the tris adduct in good yield.

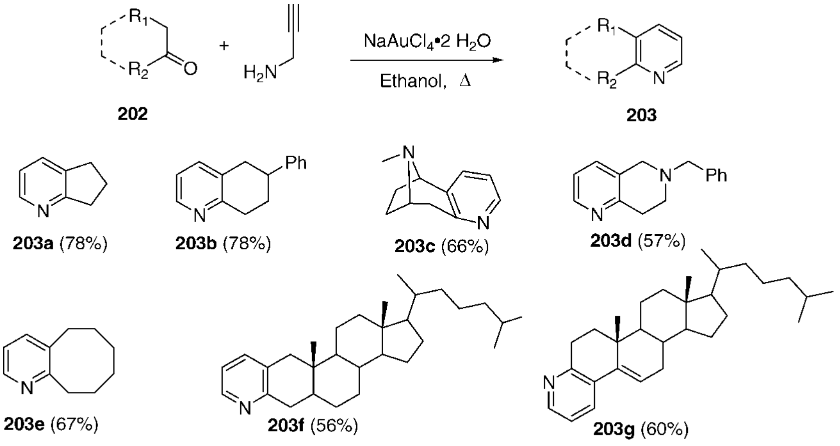
The first reaction of the carbonyl group with the electron-rich arene is the rate-limiting-step, the reaction of the benzylic alcohol is much faster. Mercury(II) perchlorate, thallium(III) perchlorate, and *p*-toluenesulfonic acid were also found to efficiently catalyze the condensation of two furans with aldehydes or acetone.[211a] While mercury and thallium salts, because of their toxicity, are not an alternative to Brønsted acids with non-nucleophilic counterions and ytterbium salts suffer from activity problems, the mild conditions of the gold catalysis are an interesting synthetic alternative. In a related study, Nair and co-workers reported that the more-reactive α,*β*-unsaturated aldehydes underwent a unusual hydroarylation with electron-rich arenes in the presence of 1% gold(III) salt, affording the tris-addition products from good to excellent yields (Scheme 131).[212]

3.2. Addition Reactions

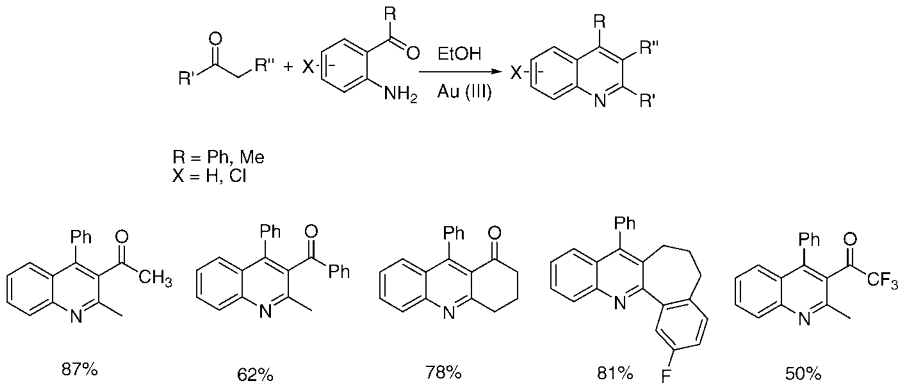
In α,*β*-unsaturated carbonyl compounds, the olefin reacts faster than the carbonyl group, while other alkenes remain intact.[213] Similarly, the reaction of α,*β*-unsaturated carbonyls with electron-rich arenes in the presence of Brønsted acids was studied,[211b,212] and the results show that better product yields and higher degrees of selectivity were observed when gold(III) chloride was used as catalyst. The different selectivities observed with Brønsted acids and gold catalysts can either be explained by specific acid catalysis or by a direct participation of the metal. Thus these experiments do not rule out a CH-activation of the aromatic system by the gold catalysts.

The acid-sensitive azulene **211** had given the double addition product **213** with gold catalyst with tremendous selectivity (Scheme 132).[214] Cycloaurated compounds **212a**

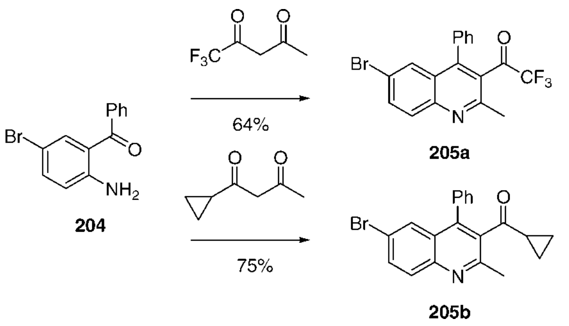
Scheme 123



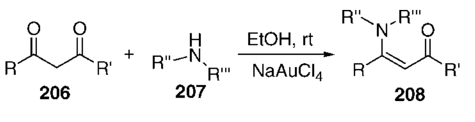
Scheme 124



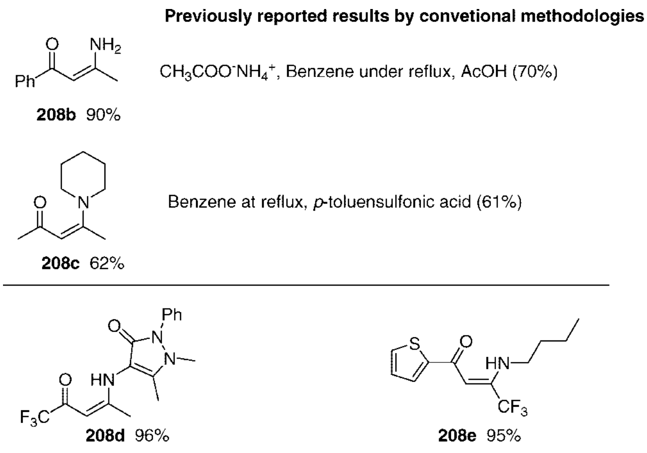
Scheme 125



Scheme 126



Scheme 127

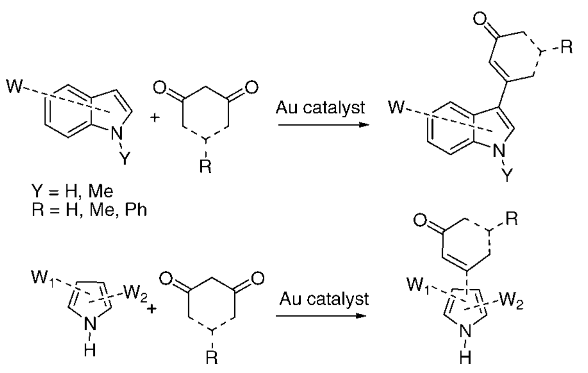


and **212b** were efficient catalysts in the presence of silver salts. It is remarkable that with AuCl$_3$ compound **213** could be obtained in only a 55% yield after 3 days, whereas for **212a** or **212b** yields of 90% can be obtained after 24 h. In this case, the more acidic character of AuCl$_3$ versus the less acidic character of **212a** or **212b** may be responsible for a lower yield. This is an indication that electronic or steric modifications of the coordination environment around the gold(III) center may result in an improved catalytic performance. The organogold(III) iminophosphorane compounds are a better alternative to AuCl$_3$ for acidic-sensitive substrates.

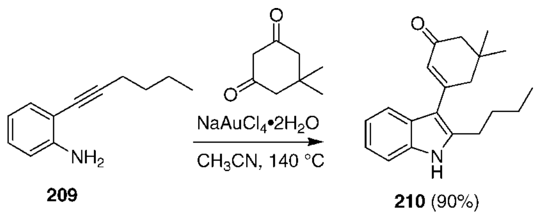
AuCl$_3$ works as an excellent catalyst to mediate reactions between various heterocycles and conjugate alkenes and alkynes under mild conditions.[215] The method tolerates different functional groups, such as aldehyde, carboxylic acid, and nitrile, and is highly efficient. Some of these reactions complete in minutes at room temperature. In this field, 3-unsubstituted indoles undergo regioselective alkylation at the 3-position of the indole nucleus through gold-catalyzed conjugated addition type reaction with α,*β*-enones. 3-Substituted indoles undergo C-2 alkylation. Sequential C-3/C-2 gold-catalyzed alkylation of the indole with dibenzylidene acetone gives a polyciclic indole *b*-annulated with a seven-membered cycle (Scheme 133).[216]

In contrast to indoles, under similar reaction conditions, pyrroles preferentially give rise to doubly substituted products. In an intramolecular competition experiment with a furan ring, only the pyrrole ring reacted (Scheme 134).[217]

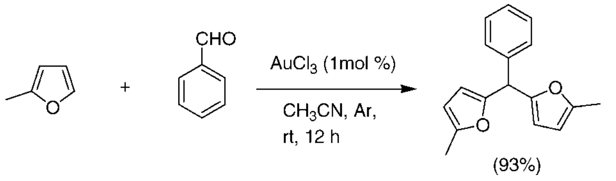
Scheme 128



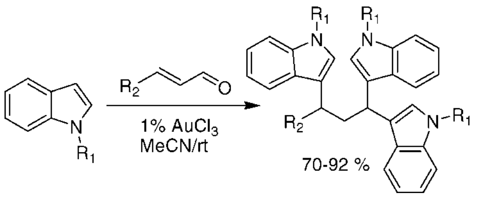
Scheme 129



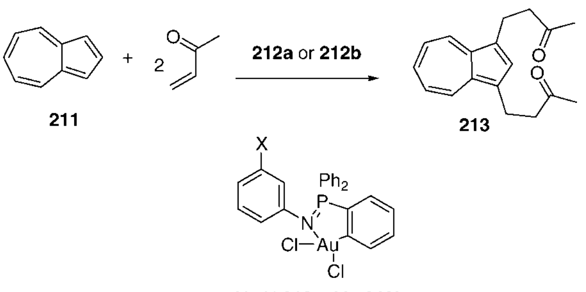
Scheme 130



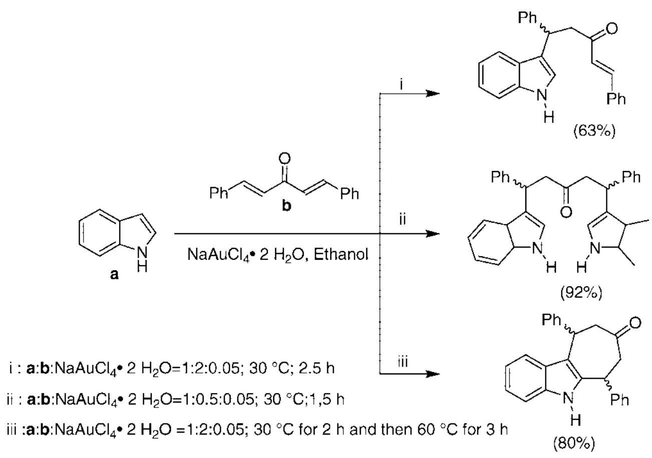
Scheme 131



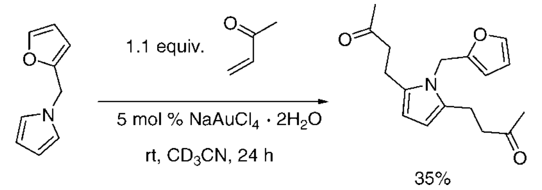
Scheme 132



Scheme 133



Scheme 134



The Au(III)-catalyzed reaction of α,*β*-enones with 7-azaindole derivatives **214** showed that steric factors on both azaindoles and α,*β*-enones seems were determinant to direct the reaction toward C-3 versus N-1-alkylation products [**215** vs **216**] (Scheme 135).[218] In particular, *β*-unsubstituted α,*β*-enones reacted with C-6 unsubstituted 7-azaindoles to give N-1-alkylated derivatives through an aza-Michael addition-type reaction, whereas the substitution on C-6 or *β*-hindered enones led to the selective C-3-alkylation of azaindole nucleus.

Nitrogen versus oxygen coordination of the gold catalyst can play a central role in the reaction outcome. The conjugate addition step could be probably promoted by gold ions, as well as protons, whereas the regiochemical outcome is determined by the sterical-dependent possibility to form two different gold−azaindole complexes (Scheme 136).

A unusual type of intramolecular nucleophilic addition to alkynes involve a formal activation of a proximate potential nucleophile (usually a carbonyl compound) by a "trigger", which typically is another nucleophile. In these reactions, the gold catalyst could theoretically carry out a double activity, enhancing the electrophilicity of both carbonylic carbon and double bond (Scheme 137).

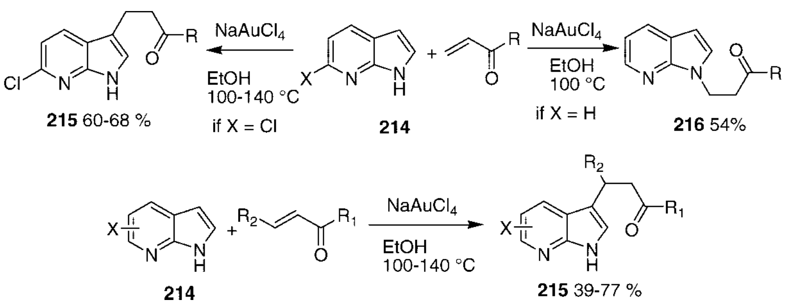
Larock et Al. envisioned that 2-(1-alkynyl)-2-alken-1-ones might undergo a gold-catalyzed cyclization to highly substituted furans.[219] Overall, ready access to a wide variety of polysubstituted furans **217** is achieved upon reaction of various 2-(1-alkynyl)-2-alken-1-ones **216** with an unprecedented set of nucleophiles under very mild reaction conditions (Scheme 138). Alcohols and 1,3-diketones, as well as various electron-rich aromatics, serve as efficient nucleophiles in this process. The cyclization of 2-(1-alkynyl)-2-alken-1-ones **216** proceeded smoothly also with a catalytic amount of $Bu_4N[AuCl_4]$ in $[bmim]BF_4$. This system is air-stable and recyclable.[220] Copper(I) salts in DMF are also efficient catalysts, but high temperatures (80 °C) were needed for the complete reaction.[221]

Liu's group synthesized a series of 3(^{2}H)-furanones **219** starting from 2-oxo-3-butynoic esters or alkynyl-1,2-diones **218** (Scheme 139).[222] The reactions proceeded smoothly under mild condition in the presence of 2% $AuCl_3$ in dichlorometane, and any additive was requested. The cationic gold complex $Ph_3PAuCl/AgBF_4$ gave similar results. When the catalyst loading was decreased to 0.1% in the model reaction, the yields were reduced to only 15%.

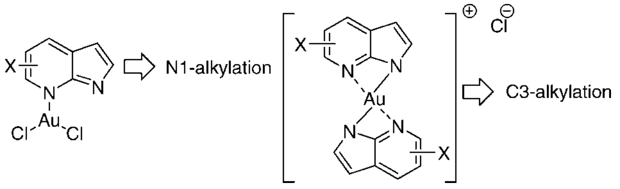
An atom-economical gold(I)-catalyzed cascade process of 1-(1-alkynyl)-cyclopropyl ketones **220** with nucleophiles allowed access to condensed ring systems **221** under ring expansion (Scheme 140).[223]

Concise synthesis of 1,3-disubstituted-1,2-dihydroisoquinolines **223** was established by tandem nucleophilic

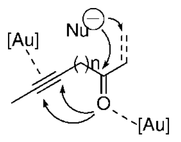
Scheme 135



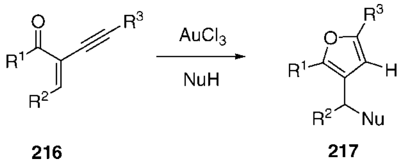
Scheme 136



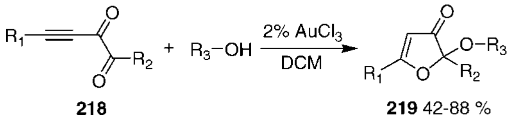
Scheme 137



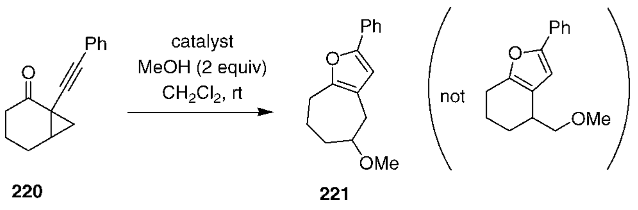
Scheme 138



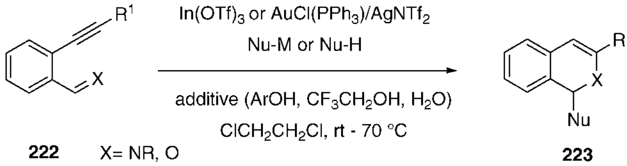
Scheme 139



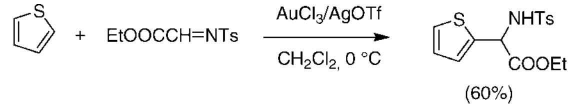
Scheme 140



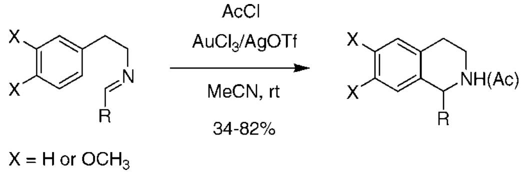
Scheme 141



Scheme 142



Scheme 143



addition and cyclization of 2-(1-alkynyl)arylaldimines **222** and various nucleophiles in the presence of carbophilic Lewis acids, such as In(OTf)$_3$, NiCl$_2$, and AuCl(PPh$_3$)/AgNTf$_2$. Among these catalysts, Au(I) catalysts requires appropriate proton sources, by which a wide range of nucleophiles and substrates can be employed for this tandem reaction (Scheme 141).[224]

A highly efficient imino Friedel−Crafts type addition of arenes to imines is developed by using a combination of gold and silver catalysts;[225] various amino acid derivatives are generated by this method. No reaction was observed by using several potential catalysts such as ZnCl$_2$, AlCl$_3$, and RuCl$_3$·3H$_2$O. Even if either AgOTf or AuCl$_3$ alone can be effective catalysts, an improvement of the yield of the desired product was observed when a combination of AuCl$_3$/AgOTf (2/6 mol%) was employed as catalytic system (Scheme 142).

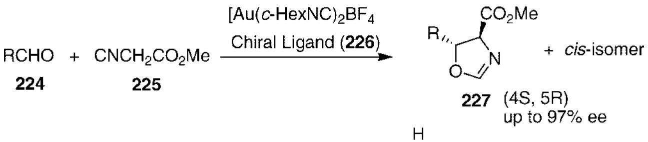
Mild and efficient AuCl$_3$/AgOTf-catalyzed Pictet−Spengler reactions were developed to afford in good yields a variety of tetrahydroisoquinoline and tetrahydro-β-carboline ring systems (Scheme 143).[226] Strong Brønsted acids are most commonly employed to promote the Pictet−Spengler reaction.[227] To enhance the reactivity of imine, an acylating agent was involved. It is likely that this reaction proceeds an electrophilic pathway involving imine activation by coordinating gold(III) complex. The process is mild and efficient and can be used to synthesize a variety of tetrahydroisoquinoline and tetrahydro-β-carboline derivatives that constitute important motifs in biologically active natural and synthetic organic compounds.

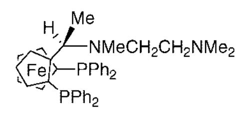
3.3. Aldol Reactions

A first landmark in gold catalysis was made by Ito and Hayashi when they reported an elegant synthesis of oxazolines **227** using a gold(I)-catalyzed aldol reaction in the presence of chiral ferrocenylamine ligands **226** that possess both planar and central chirality (Scheme 144).[228]

Mechanistic aspects of this gold(I)-catalyzed aldol reaction were investigated. It was proposed that the terminal amino group of pendant side chain of ferrocenylphosphine ligand **226** participates in the formation of enolate of the isocyanate coordinated with gold and the participation permits a favorable arrangements of enolate and aldehyde on the gold at the stereodifferentiating transition state to bring about high stereoselectivity (Scheme 144, figure A).[229] On the basis of

Scheme 144





226

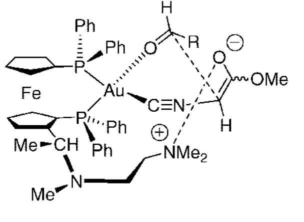
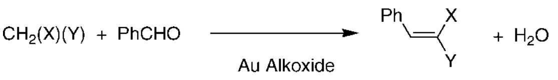


Figure A

Scheme 145



X = CN; Y = COOMe, COOEt
X = H; Y = COPh
X = CN; Y = CN

the proposed mechanism, appropriate modification of the terminal amino group of the ligand increased the stereoselectivity. The ferrocenylphosphine ligand containing morpholino or piperidino group at the end of ferrocene side chain gave the best results.[230] Aldol reaction of **225** with paraformaldehyde in the presence of 1% of a chiral (aminoalkyl)ferrocenylphosphine-gol(I) complex gave optically active 4-alkyl-2-oxazoline-4-carboxilates (up to 83% ee), which were readily hydrolyzed to α-alkylserines.[231] Asymmetric aldol reaction of **225** with (*E*)-2-hexandecenal in the presence of 1 mol % of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex afforded optically active *trans*-4-(methoxycarbonyl)-5-((*E*)-1-pentadecenyl)-2-oxazoline (93% ee), which was readily converted into *D*-threo- and erythro-sphingosines.[232]

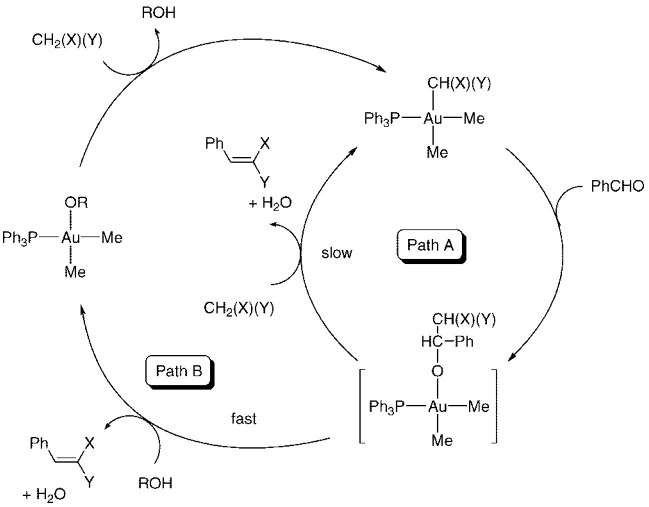
Gold-catalyzed Knoevenagel reactions (Scheme 145) can be carried out in the presence of catalytic amounts of gold alkoxides under neutral and mild conditions, where the catalytic activity and selectivity of the reaction may be controlled by changing the properties of the alkoxides, ligands, and the valency of the metal.[233]

Gold(I) complexes show higher catalytic activity than gold(III). C-bonded gold complexes can be isolated from the reactions of gold alkoxides with the corresponding active methylene compounds. A reaction mechanism involving two catalytic pathways has been proposed (Scheme 146).

The $AuCl_3-PPh_3$-, and $AuCl_3$-catalyzed direct Mannich reactions of aryl aldehydes **228**, aryl ketones **229**, and carbamates led to the synthesis of N-protected *β*-aryl-*β*-amino ketones **230** (Scheme 147).[234]

The formation of imine from carbamate with aldehyde was easily catalyzed by the gold catalyst, and the aldol reactions of benzaldehyde or imine with acetophenone could be carried out with the same gold catalyst. In these different reactions, the formation of imine was a faster step. From a synthetic point of view, one-pot three-component reaction represents an atom-economical synthetic method, as well as a useful method, for the facile synthesis of *β*-amino ketone libraries (Scheme 148).

Scheme 146



3.4. Hydro- and Carbosilylation Reactions

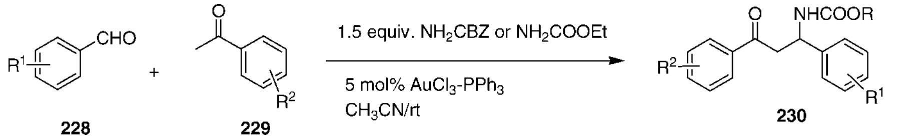
Hydrosilylation of aldehydes and ketones is an important reaction for the preparation of various intermediates in organic synthesis and is generally catalyzed by rhodium, ruthenium, or platinum complexes.[235] Hosomi and coworkers[236] showed the possibility to hydrosilylate aldehydes with $[(PPh_3)AuCl]$ (Scheme 149).

The reducing power of silane destabilizes the gold(I) catalyst giving rise to gold clusters or particles, and a large excess (20%) of Et_3P, *n*-Bu_3P, or *t*-Bu_3P proved to be optimal for high conversion at 24 °C.[237] In situ IR and NMR experiments have revealed that both the ligand and the substrate aldehyde play an important role in stabilizing the gold catalyst and forming the catalytically active species. Several side reactions involving water and oxygen were also investigated. A plausible reaction pathway as an alternative to the well-accepted mechanism for the transition-metal homogeneously catalyzed hydrosilylation of aldehydes has been proposed to accommodate the experimental observations.[238]Au(I) complexes supported by donor-functionalized indene ligands[237] **235**, as well as pyridine ONN-pincer[239] gold **237**, were synthesized, and their behavior in hydrosililation carbonyl compounds was evaluated (Scheme 150). The pyridine ONN-pincer gold catalysts were shown to be very active. The reactions were carried out with carbonyl compound (1 mmol)/silane (2 mmol), and the gold catalyst (5%) in toluene (1 mL) at 70 °C under a nitrogen atmosphere.

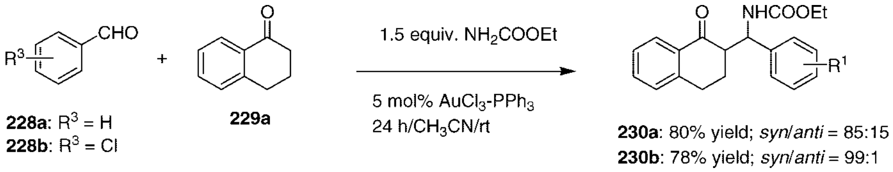
The facile recycling of gold hydrosilylation catalyst can be achieved by using fluorous phosphine-modified gold complexes.[240] To achieve effective product separation, the known ($AuCl(PPh_3)/n$-PBu_3, $n = 6$) catalyst system has been modified by fluorous phosphines which permit the application of fluorous biphasic or thermomorphic protocols. The addition of fluorous phosphines $[P\{(CH_2)_nC_8F_{17}\}_3]$ ($n = 3$ (**238a**) and 4 (**238b**)) to [AuCl(tht)] (tht = tetrahydrothiophene) in CH_2Cl_2 was used for the preparation of the fluorous gold(I) compounds **239** (Scheme 151).

The fluorous gold(I) compounds **239** are air-stable white solids that can be stored at room temperature for several months without decomposition. They are soluble in fluorous solvents at room temperature and were tested in the biphasic hydrosilylation of benzaldehyde. The experiments were carried out under biphasic conditions using FC-72 or perfluoroheptane as the fluorous phase containing the catalyst.

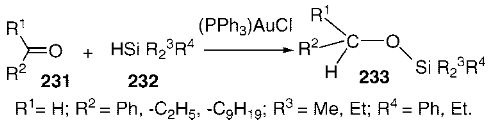
Scheme 147



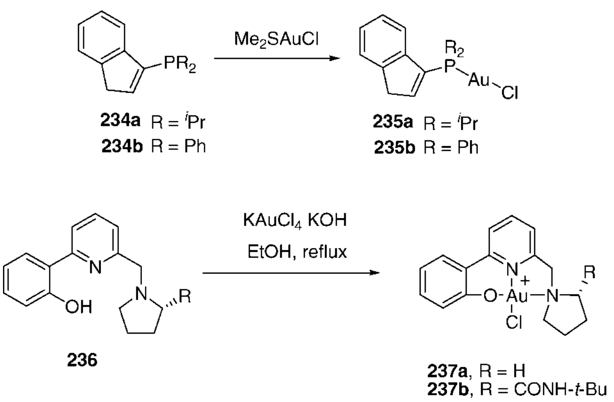
Scheme 148



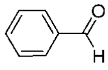
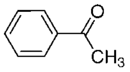
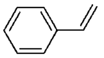
Scheme 149



Scheme 150



Gold-Catalyzed Hydrosilylation with Ph$_2$SiH$_2$

Catalyst			
237a	90%	70%	50%
237b	80%	50%	40%

Scheme 151

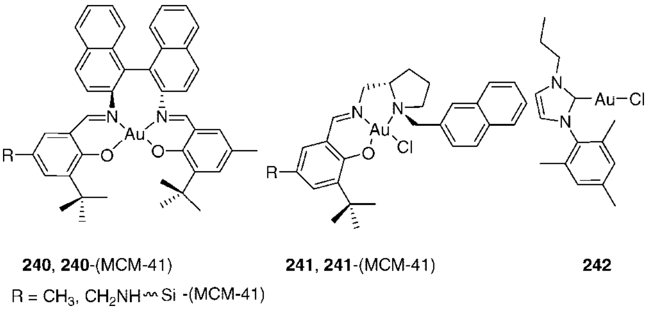
$$[\mathrm{AuCl(tht)}] + \mathrm{P((CH_2)_nC_8F_{17})_3} \xrightarrow[\mathrm{-(tht)}]{\mathrm{dry\ CH_2Cl_2,\ rt}} [\mathrm{AuCl\{\,P((CH_2)_nC_8F_{17})_3\,\}}]$$

n= 3 (**238a**), 4 (**238b**) n= 3 (**239a**), 4 (**239b**)

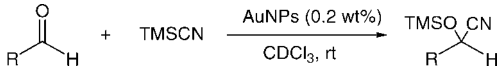
Nanoparticles of gold, on carriers that are able to stabilize cationic forms of gold, can be a general recyclable catalyst for the hydrosilylation of a large variety of functionalities (aldehydes, ketones, olefins, imines, and alkynes).[241] To find which, among Au(I), Au(III), and Au(0) species, are the active sites for hydrosilylation, a series of Au(I) ([(PPh$_3$)AuCl], [(carbene)AuCl] (**242**), and [(tht)AuCl]; tht = tetrahydrothiophene) and Au(III) complexes (**240**, **241**) (Scheme 152) and salts (KAuCl$_4$), as well as colloidal Au(0) with a mean diameter of 5 nm, have been tested.

Au (I) and, especially, Au (III) species are both active for the hydrosilylation of carbonyl compounds and olefins, while nanoparticles of metallic gold (colloidal Au) are only active for the hydrosilylation of carbonyls. It is noteworthy that Au/CeO$_2$, as well as the homogeneous catalysts studied, is chemoselective for the hydrosilylation of the carbonyl group.

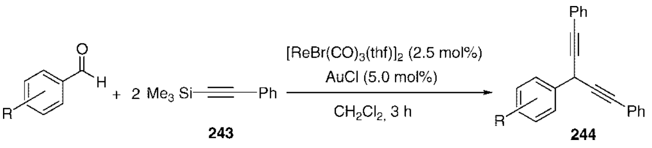
Scheme 152



Scheme 153



Scheme 154

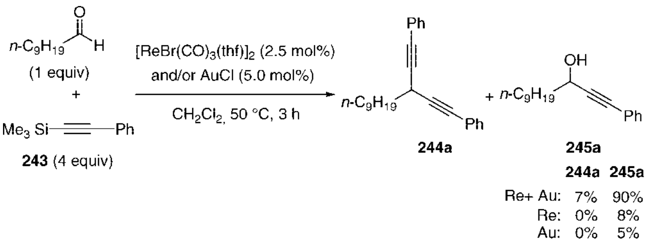


Moreover, when the Schiff base Au(III) complexes, **240**−**241**, are grafted on a mesoporous MCM-41 support, they are active and chemoselective, and can be recycled without any decrease in activity. Gold nanoparticles (AuNPs) of zero oxidation state [Au(0)] are catalytically active for the cyanosilylation of aldehydes (Scheme 153).[242] The reactions of aromatic aldehydes were almost quantitative, except for benzaldehyde derivatives containing the electron-withdrawing NO$_2$ group, and α,β-unsaturated aromatic aldehydes were the most reactive substrates. The reactions also went smoothly for aliphatic aldehydes. Mechanistic studies indicated that the reactions proceeded both homogeneously and heterogeneously.

Synthetic reactions using a combination of two metal complexes have received considerable attention because they lead to products that cannot be synthesized with only one of the catalysts.[243] Treatment of benzaldehyde with trimethyl(phenylethynyl) silane **243** in the presence of a catalytic amount of the rhenium complex, [{ReBr(CO)$_3$(thf)}$_2$] (2.5 mol%) and AuCl (5.0 mol%) gave diethynylmethane **244** in 72% yield (Scheme 154).[244]

The yield of **244** increased slightly with use of twice the amounts of rhenium and gold catalysts. The reaction proceeds via propargyl alcohols **245** as intermediates (Scheme 155).

Scheme 155



	244a	245a
Re+ Au:	7%	90%
Re:	0%	8%
Au:	0%	5%

A combination of the rhenium and gold complexes promotes the first ethynylation step, and the rhenium complex accelerates the second ethynylation (Scheme 156).

3.5. Nucleophilic Substitution Reactions of Alcohols

Nucleophilic substitution of propagylic and allylic substrates represents a powerful method for producing useful synthetic intermediates. Readily available allylic and propargylic alcohols are desirable substrates for the synthesis of allylic and propargylic amines. Substitution of the hydroxy group in alcohols by amine nucleophiles generally requires preactivation of the alcohols because of the poor leaving ability of the hydroxy group. Alcohols are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds with good leaving groups. The process inevitably produces a stoichiometric amount of salt waste. The substitution of the halides and related compounds also produces salt waste and requires a stoichiometric amount of a base. In this context, allylic aminations of allylic acetates and their derivatives have intrinsic drawbacks in terms of atom economy. Therefore, the direct catalytic substitution of alcohols with amines is desirable. Because no stoichiometric hydroxyl group activator is used, the products are produced with water as the only waste. A number of direct allylic aminations catalyzed by transition metals have been reported.[245] However, in most cases, either a high reaction temperature is required or a promoter is added to enhance the leaving ability of the hydroxy group. Gold catalysts have been reported to act as propargylic alcohol activating agents in propargylic substitutions (Scheme 157).[246]

The Au(III)-catalyzed reaction was tested for a diverse collection of nucleophiles. The corresponding propargylic ethers were obtained, using alcohols, in good yields. Thiols act as efficient nucleophiles to give the corresponding sulfides in modest to good yields. In the presence of electron-rich aromatic compounds, Friedel–Crafts arylation occurs to give the arylated compounds in good yields. Modifications on the alkynyl part are also allowed because silyl and aryl substituents are well tolerated. Finally, nonbenzylic and tertiary propargylic alcohols can also act as efficient substrates in these reactions. The reaction proved to be efficient with various Au(III) catalysts (5%). The best results were observed with $NaAuCl_4 \cdot 2H_2O$, and this allowed the reduction of the amount of catalyst to 1%. In the presence of Au(I) catalysts, more disappointing results were obtained. Finally, no reaction occurred under the same reaction conditions in the presence of $PtCl_2$ and $PdCl_2(PhCN)_2$ catalysts. In the presence of ethanol (Scheme 158) and 5% of $NaAuCl_4 \cdot 2H_2O$, the rearranged unsaturated ketones **247** are obtained in good yields. However, starting from **245a** with only 1% of catalyst, the reaction can be stopped at the ether stage **246a** obtained in 60% yield (Scheme 158).

A mechanism involving the formation of a carbonium intermediate has been suggested because of the observed racemization in the substituted derivative when starting from an enantiomerically enriched propargylic alcohol.

Direct amination of allylic alcohols offers a straightforward route to substituted allylic amines.[247] Treatment of a mixture of diphenylprop-2-en-1-ol **248** and 2 equiv of $TsNH_2$ with 2 mol% $AuCl_3$ in anhydrous MeCN afforded the corresponding allyl sulfonamide **249** smoothly in 87% isolated yield, after the mixture was stirred for 30 min at room temperature. Reduction of the amount of $TsNH_2$ to 1 equiv resulted in a lower yield (67%) of **249** after three hours. The cationic gold(I) complex $AuCl(PPh_3)$/AgOTf also showed good catalytic activity in THF to afford 76% of **249**; however, a prolonged reaction time (12 h) was required (Scheme 159).

The method has been applied successfully to various types of cyclic and acyclic allylic alcohols to provide the allylic amines in 58–96% yields. Trisubstituted olefins reacted with tosylamine ($TsNH_2$) smoothly to generate the corresponding allylic amine derivative in high regio- and stereoselectivity. However, in these cases, at least 4 equiv of the amine nucleophile were required to achieve a clean transformation. Gold(III) proved to be the catalyst of choice in the direct amination of benzhydryl alcohols **250** for both chemical (yield, conversion) and practical reasons (a filtration over a silica pad is generally sufficient to obtain the corresponding benzylic amine **251** in analytically pure form) (Scheme 160).[248] The benzhydryl alcohol **250** in the presence of $TsNH_2$ in the presence of $NaAuCl_4 \cdot 2H_2O$ gave the amination product **251** in 95% yield. Because of the complete conversion of the starting material, combined with the absence of side-products, analytically pure **251** was easily isolated by simple filtration over a silica pad. In the absence of tosylamine, the corresponding ether **252** was obtained in quantitative yield. The less Lewis acidic gold(I) was inefficient in this reaction. Ti(IV) afforded the expected amination product **251** in a poor 37% yield; In(III) and $BF_3 \cdot OEt_2$ were equally efficient leading to **251** in 87 and 85% yields, respectively. Slightly lower yields were obtained with indium and $BF_3 \cdot OEt_2$ compared to those obtained with $NaAuCl_4$, mainly because of the presence of traces of both starting material and ether **252** in the crude product.

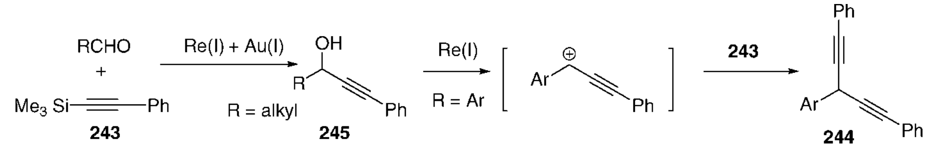
Several other N-nucleophiles including 2,4-dinitrophenylhydrazine, 4-nitroaniline, and trimethylsilyl azide were successfully tested, allowing the introduction of hydrazine and aniline-based, as well as azido, moieties at the benzylic position (Scheme 161).

The reaction was tested on other benzylic substrates. When 1-phenylethanol **260** was reacted with tosylamine in the presence of $NaAuCl_4$, the desired amination product **261**was obtained in 87% yield. In contrast, benzyl alcohol **262** was recovered unchanged even after prolonged reactions times (Scheme 162).

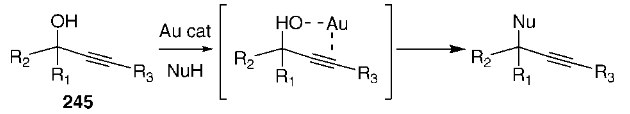
4. Gold-Catalyzed C–H Bond Functionalization

Catalytic C–H activation and functionalization by metal complexes is a hot topic in organic chemistry and of growing importance for organic synthesis.[249a,b] In the past few years, gold has been recognized to be a very active in this field. Cationic gold catalyzes the selective, low-temperature, oxidation of methane to methanol in strong acid solvent using Se^{VI} ions as the stoichiometric oxidant.[249c] The reaction does not appear to proceed through free radicals, and DFT calculations indicate that Au(I) or Au(III) species are both

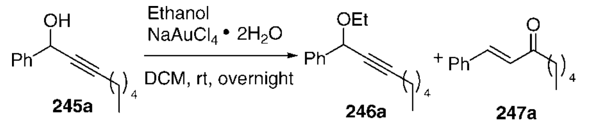
Scheme 156



Scheme 157

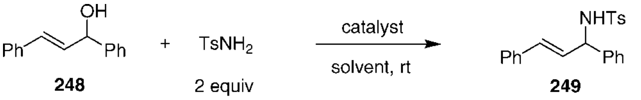


Scheme 158



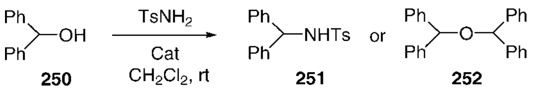
	246a	247a
5% cat	-	58%
1% cat	60%	35%

Scheme 159

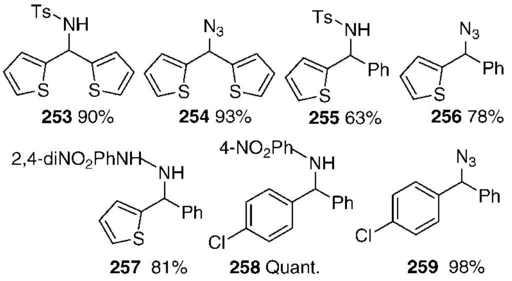


catalyst	yield (%) of **249**
2% $AuCl_3$, MeCN, 30 min	87
5% $(PPh_3)AuCl/AgOTf$, THF, 12 h	76

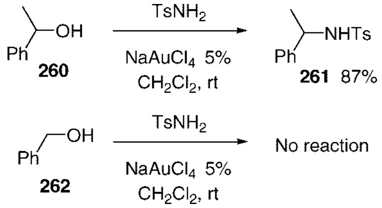
Scheme 160



Scheme 161

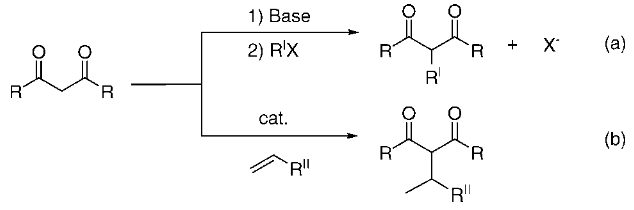


Scheme 162



viable catalysts that operate by mechanisms involving overall electrophilic C−H activation and oxidative functionalization. Ionic gold catalyzes the oxidation of alkanes with H_2O_2 to alkyl hydroperoxides, for example, but this is probably a free radical process.[249d,e] Direct α-auration of carbonyl derivatives was observed.[249f] The electrophilic metalation of arenes by gold(III) was known a long time ago. It was speculated that the arylgold(III) species obtained from an auration process might react with different substrates to construct C−C bonds.

Scheme 163



Gold(I) and gold(III) salts are able to activate C−H bonds of terminal alkynes, thus forming nucleophiles which can react with various electrophiles. The latter can also be activated by the Lewis-acidic gold catalyst, which therefore might play a dual role in these transformations. Most recently, the finding that C−N bond formation can be catalyzed from direct functionalization of aromatic and benzylic C−H groups is adding new and exciting activity to this chemistry.

4.1. C_{sp^3}−H Bond Functionalization

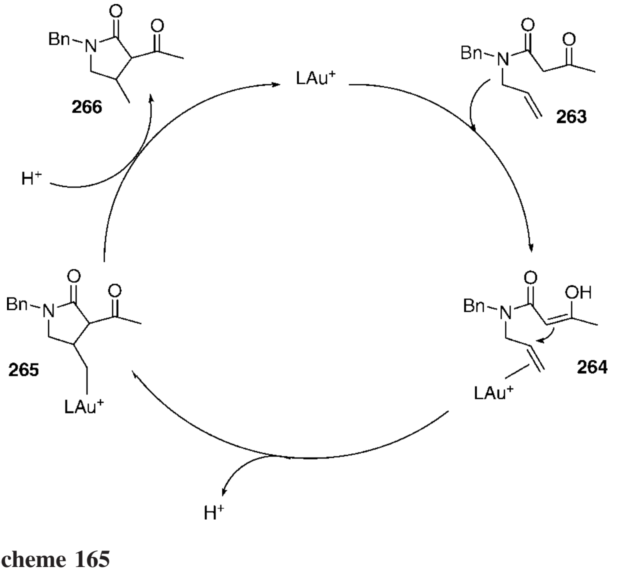
One of the most common methodologies for the formation of carbon−carbon bonds, the alkylation of 1,3-dicarbonyl compounds usually requires the use of a stoichiometric amount of base and an organic halide (Scheme 163a). An alternative reaction via metal-catalyzed addition of 1,3-dicarbonyl compounds to alkenes would provide a more atom-economical approach and has attracted much interest.[250] A highly effective and practical intermolecular addition of activated methylene compounds to alkenes was developed by using $AuCl_3/AgOTf$ (Scheme 163b).[251]

Changing the counterion of the silver salt from OTf, lowered the yield, but no difference was observed when the counterion of the gold was changed. CH_2Cl_2 was the solvent of choice. A side reaction observed was the polymerization of the starting alkene. Increasing the excess of alkene could be beneficial. Dimerization of styrene became more serious problem with an increase in the reaction scale. The use of a more diluted solution and a slower addition helped to inhibit the dimerization process. The reaction was reversible at higher temperatures.[252] In small-scale reactions, the reversibility was not a serious problem. However, for large-scale reactions, the catalyst had to be removed by a short silica gel column before concentration. Under the same conditions, various cyclic dienes and cyclic enol ethers were also reacted.[253]

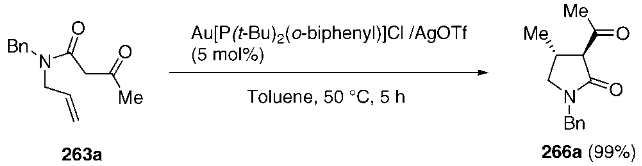
Au(I) complexes efficiently catalyze intramolecular addition of *β*-ketoamide to unactivated alkenes to afford highly substituted lactams **266** (Scheme 164); the latter are commonly found in natural products and biologically active molecules.[254] A variety of substrates underwent Au(I)-catalyzed exo-trig cyclization to give highly substituted lactams. In all cases, no endo-cyclization was observed.

The protocol with 5 mol % of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf at 50 °C in toluene gave the best results. Under these conditions, the *β*-ketoamide **263a** gave the product **266a** in 99% yield after 5 h. The trans stereochemistry of **266a** was

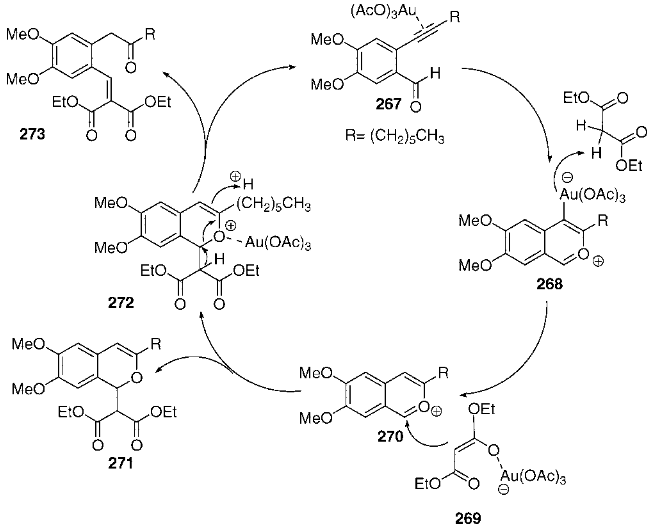
Scheme 164



Scheme 165



Scheme 166



proposed by comparison with that of related compounds (Scheme 165). The catalysis also could be performed in a preparative-scale and in aqueous media: the reaction using 5 g of substrate **263a** and with 1 mol % of catalyst loading gave product **266a** (4.5 g) in 90% yield.

Gold might play a dual role catalysis. Multidimensional reaction screening of *o*-alkynyl benzaldehydes with a variety of catalysts and reaction partners led to identification of new chemical reactions.[255] A promising reaction discovered in the screening process was cycloisomerization/nucleophilic addition using diethyl malonate. Scheme 166 outlines a proposed pathway for cycloisomerization/nucleophilic addition to afford isochromene **271** and benzylidenemalonate **273**. Optimization of the reaction conditions showed that use of 10 mol % of $Au(OAc)_3$ and microwave irradiation (110 °C, 10 min) afforded **271** (62%) along with ring-opened product **273** (20%). Use of CH_3CN as solvent produced exclusively **273** (90% yield).

Toste and co-workers applied phosphine–gold(I) complexes in the carbocyclization of β-keto esters with alkynes (also called the Conia-ene reaction) under mild and neutral conditions.[256] Tris[(triarylsilyl)ethynyl]phosphines **274** bearing bulky end caps at the alkyne termini were synthesized, and their most salient feature was the holey molecular shape possessing a deep and large-scale metal-binding cavity (Scheme 167).

The holey phosphines displayed remarkable rate enhancement and marked advantage over conventional phosphine ligands in the gold(I)-catalyzed six- and seven-membered ring forming cyclizations of acetylenic keto esters **271** (Scheme 168). It was proposed that the cavity in the ligand forces a nucleophilic center (enol or alkene) of the acetylenic compounds close to the gold-bound alkyne.[257]

Bulky *N,N′*-disubstituted cyclic thiourea ligands have been, also, applied in the gold(I)-catalyzed cycloisomerization of 1,3-dicarbonyl compounds with alkynes accomplishing a high level of diastereoselectivity. The combination of **277** with silver triflate has been found to be an excellent catalyst for the Conia-ene cyclization of 1,3-dicarbonyl compounds **278**. The reactions can be readily conducted in high yield under mild and neutral conditions with a low catalytic loading in an "open flask" system (Scheme 169).[258]

Gold-catalyzed C–H activation at a benzylic position can take place in a neutral solvent at room temperature.[259] The starting point was the gold-catalyzed conversion of substrates **281**, which underwent the expected 6-endo-dig cyclization to give isochromene derivatives **282** (Scheme 170).

When the substrates **281** bore additional nucleophilic groups like ester or amide functionalities not only product **282** but also, through the formation of eight new bonds, the unexpected dimer **283** were obtained with both the gold(I) and the gold(III) catalysts (Scheme 171).

A mechanistic proposal for the formation of **283** is depicted in Scheme 172.

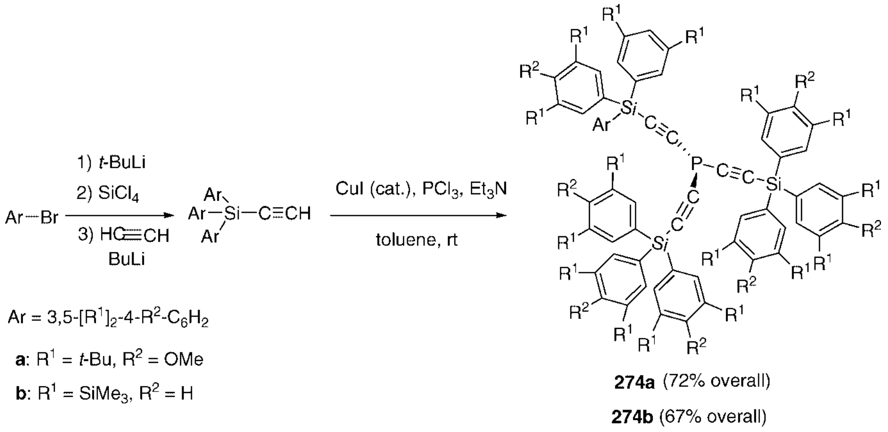
Either the hydroxy group can attack as a nucleophile (path a), or the second nucleophilic group can attack (path b). The nucleophilic attack of the carbonyl group and a subsequent protodemetalation would lead to the olefin complex **284**, which then could deliver **285** by an intramolecular addition of the hydroxy group. Intermediate **285** represents an activated derivative of the benzyl alcohol. Attack of a second molecule of **281a** would then form the dibenzyl ether **286**. The conversion of **286** into **283** should proceed by electrophilic C–H activation (Scheme 173), possibly assisted by the carbonyl group as an additional ligand.

Crucial information regarding the mechanism came from attempts to recrystallize a $[(Mes_3P)AuX]$ catalyst from acetone. In this situation, the carbonyl compound was present in high concentration, and a direct α-auration was observed. In the light of previous reports on C–H activation assisted by coordinating groups at higher temperatures,[260] this indicates that gold-catalyzed C–H activation, when directed by proper coordination/chelation, should generally proceed under very mild conditions.

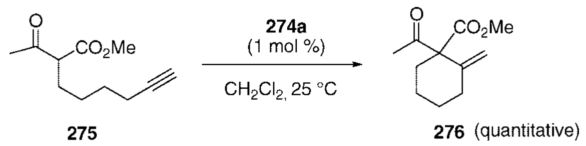
4.2. C_{sp^2}–H Bond Functionalization

Inter and intramolecular hydroarylation of alkynes[261] (or alkenylation of arenes) represent an attractive tool for the formation of new C–C bond. The mechanism involved in these transformations is the subject of continuous investiga-

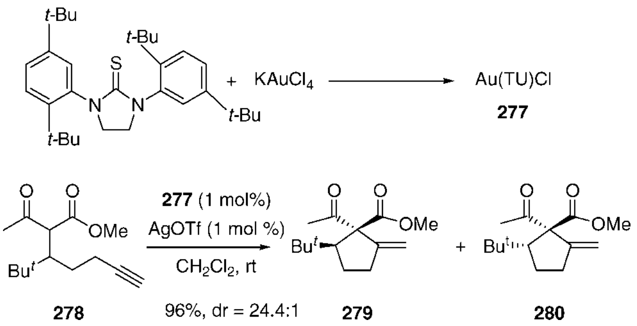
Scheme 167



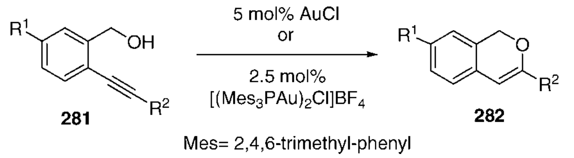
Scheme 168



Scheme 169

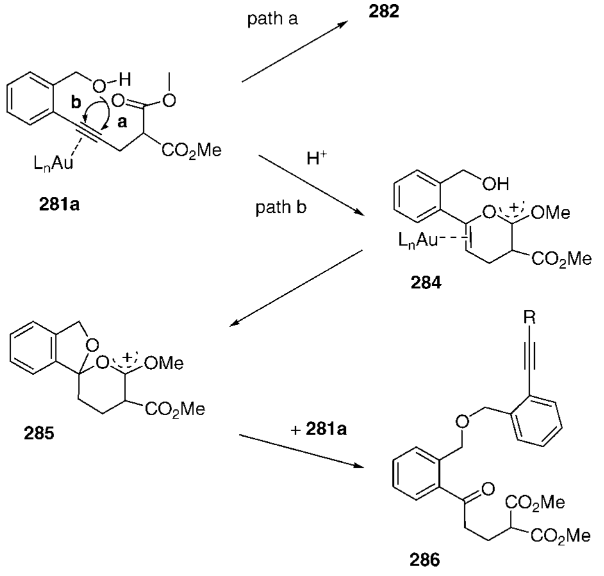


Scheme 170

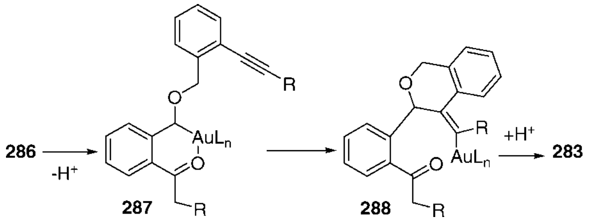


Scheme 171

Scheme 172



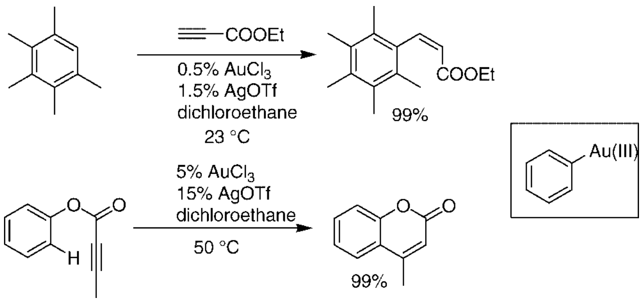
Scheme 173



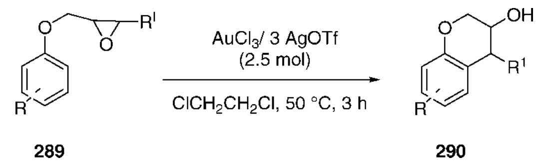
tions, also at theoretical level.[262] Although other metal catalysts such as palladium, platinum, zirconium and scandium salts are also active (and in some cases more effective) in the hydroarylation of alkynes, gold can often provide comparable or best results but with a lower catalyst loading. Spectroscopic and isotope labeling experiments reported by Shi and He[263] seemed indicate the involvement of an arene-gold intermediate in the hydroarylation reaction. In 1931, Kharasch and Isbell demonstrated that anhydrous gold(III) chloride can react with neat benzene, toluene, or other aromatic compounds to form arylgold(III) complexes at room temperature.[264] Subsequent studies of this chemistry led to the isolation and characterization of several arylgold(III) species generated from the reaction.[265] This auration reaction was shown to proceed in an electrophilic manner or by base-promoted transmetalation of aryl boronic acid.[266] Nevertheless, Shi and He did not exclude that the process could still be aided by Lewis acid-activation of alkyne promoted by metal ions or protons. The authors studied both inter- and intramolecular hydroarylation of electron-deficient alkynes. The intermolecular reactions run smoothly at rt even under solvent-free conditions in the presence of small amounts of $AuCl_3$ and AgOTf, whereas the intramolecular application to led coumarins requested higher temperature and higher catalyst loading (Scheme 174).

He's group also discovered a gold-catalyzed alkylation of arenes with epoxides. Treating (phenoxymethyl)oxiranes **289** with $AuCl_3$/3AgOTf (2.5% based on gold) in dichloroethane yielded exclusively the endo addition product 3-chromanols **290** in good yield (Scheme 175).

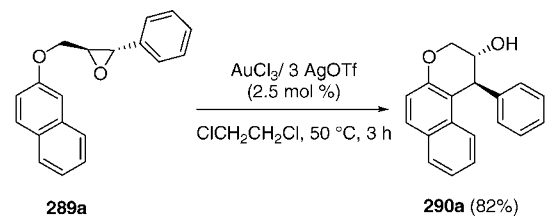
Scheme 174



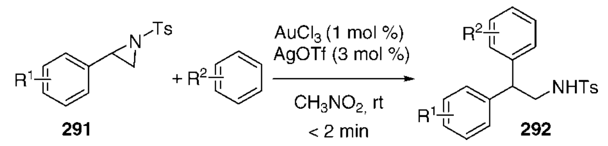
Scheme 175



Scheme 176



Scheme 177

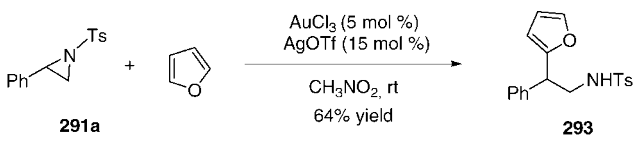


The reaction was completed at 50 °C for more electron-rich arene substrates. For less-electron-rich substrates, higher temperatures and longer reaction times were required. The reaction tolerated halide substituents, which is useful for further functionalization of the ring. The reaction showed high diatereoselectivity with trans products obtained exclusively. The inversion of configuration of the carbon atom linked to the aryl ring was confirmed by X-ray analysis. Considering that the stereochemistry of the starting epoxide is relatively easy to control; thus, the method offers a good way to access 3-chromanols stereospecifically (Scheme 176).

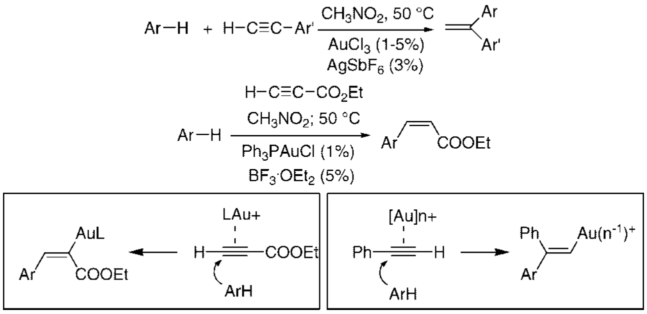
Gold(III) chloride/silver triflate was found to be a highly efficient catalyst in the ring-opening of aziridines **291**with electron-rich arenes and the desired β-arylamines **292** were afforded in good to excellent yields under mild reaction conditions (Scheme 177).[267]

$BF_3 \cdot OEt_2$ promoted reactions of aziridines with arenes has been previously reported.[268] However, 1.0 equiv of $BF_3 \cdot OEt_2$ had to be used. Indium triflate was also employed for the reaction of aziridines with arenes.[269] The reaction was usually completed in several hours in the presence of catalytic amount of $In(OTf)_3$ (5−10 mol%) and afforded the product as a mixture of regioisomers in most of cases. Reaction of aziridine **291a** with a heterocycle, such as furan, proceeded smoothly to give the desired product **293** in 2 min in 64% yield with excellent regioselectivity (Scheme 178).

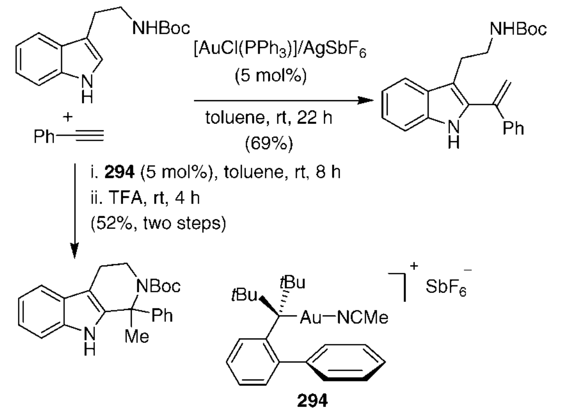
Scheme 178



Scheme 179



Scheme 180



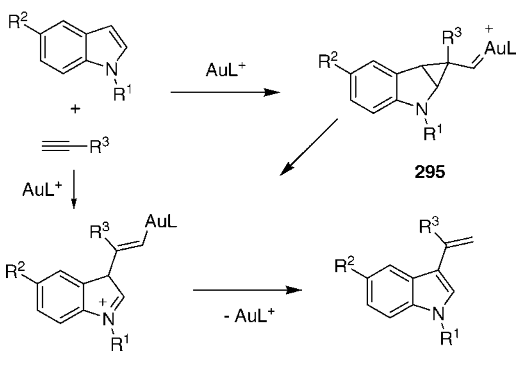
Mechanistic studies indicate the involvement of the arylgold(III) species as the reaction intermediate in the intramolecular direct functionalization of arenes by gold-catalyzed primary alcohol sulfonate/triflate esters displacement.[270]

Cationic forms of Au(III) catalyze the hydroarylation of aryl-substituted terminal alkynes. The gold(I) complex Ph_3PAuCl seemed to be the better choice for the hydroarylation of electron poor alkynes. In both cases, the presence of cocatalysts as a silver salt or boron trifluoride was necessary to achieve good yields. The authors did not believe that the mechanism involved the arene auration with formation of an organo-gold species and proposed a path involving the gold activation of the triple bond, thus forming an Au−π-complex as postulated for other gold-catalyzed nucleophilic additions to alkynes. The regioselectivity observed was determined by electronic factors (Scheme 179).[271]

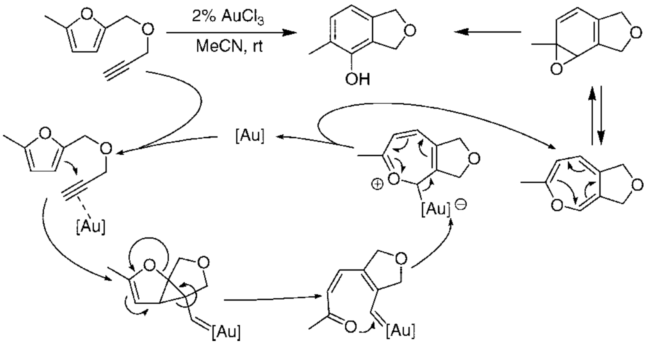
The intermolecular reaction of indoles with alkynes is also a general transformation that gives rise to products that arise from intermediate 2- or 3-alkenylindoles which often react with a second molecule of indole, alkenyl indole, or other nucleophile. Indoles that are substituted at the 3-position react intermolecularly with alkynes to give 2-alkenylated intermediates that can be trapped intramolecularly with the appropriate nucleophiles (Scheme 180).[272]

Indoles react intramolecularly with alkynes in the presence of gold catalysts to give from six- to eight-membered ring annulated compounds. The best catalyst tested for the formation of seven member rings was the easily accessible and air-stable cationic gold(I) complex **294**, which allows the cyclization to be performed in the absence of Ag(I) salts.

Scheme 181



Scheme 182



In the intermolecular reactions, an cyclopropyl metal carbene intermediates **295** may be formed (Scheme 181).

Hashmi's group developed an effective general entry to fused phenols starting from ω-alkynyl furans, using $AuCl_3$ as catalyst. According to experimental and theoretical studies, the phenol synthesis proceeds by nucleophilic attack of the furan on the alkyne−Au complex to form a carbene. After the cleavage of the C−C and the C−O bonds of the tricyclic intermediate, a new carbene is formed, which cyclizes to form a new bicyclic species. The elimination of the metal forms the oxepine, which is in equilibrium with the arene oxide, whose opening leads to the formation of phenol. The oxepines and arene oxides intermediate have been experimentally recognized in the reaction catalyzed by Au(III) (Scheme 182).[273]

Various aspects of this reaction, including catalyst selectivity and activity and the simple conditions used have been summarized.[274] Instead of the simple $AuCl_3$ a range of other gold complexes and other solvents was evaluated. This led to use of pyridine-type ligands, for example the anionic pyridine-2- carboxylato ligands **296**−**300** shown in Scheme 183. With these ligands the catalyst loading could be reduced to as little as 0.07 mol %, the yield obtained then corresponded to a TON of 1200.

Heterogeneous Au on nanocrystalline CeO_2 could also be used.[275] The influence of functional groups[276] and sterically demanding substituents[277] has been in-depth investigated. Au(I),[278] and Pt(II)[279] catalysts proved to be also effective in this reaction. The versatile approach has been applied to a variety of five-member-ring and six-member-ring fused phenols,[280] enantiomerically pure tetrahydroisoquinolines,[281] bisphenols,[282] and oxepins.[283] Interestingly, the $AuCl_3$ or $[(Ph_3PAu)_2Cl][BF_4]$-catalyzed hydroarylation of sylilated γ-alkynylfurans **301** was observed (Scheme 184).[284] Conversely, with $PtCl_2(MeCN)_2$ phenols with a silyl group were formed.

It is worth noting that using the binuclear gold(I) complex **303** (the Schmidbaur−Bayler salt) with 2,5-disubstituted furans, Hashmi and co-workers reported for the first time the formation of a gold carbenoid intermediate from an intermolecular pathway.[285] The reaction proceeded in moderate yields delivering a mixture of phenol along with a small amount of the hydroarylation product (Scheme 185).

On the other hand, under the same reaction conditions but in the presence of 2-monosubstituted furans, only the formation of the 2-fold hydroarylation product has been observed (Scheme 186).[286]

On the basis of the recent findings on cationic gold promoted 1,2-migration of the acetate group in propargylic acetates,[287] Nolan and co-workers developed a mild entry to indene nucleus starting from easily available aryl propargyl acetates.[288] Best results were obtained using a only 2% mol of the original catalytic system constituted by equimolar amount of $AgBF_4$and a NHC gold(I) complex (NHC = N-heterocyclic carbene). The reaction was found compatible with both electron-poor and electron-rich arenes, highly chemoselective and also tertiary acetates are tolerate. In some cases, isomeric indenes were also obtained as minor products. Nevertheless, the behavior of the catalysts seems to be strongly influenced by the substitution pattern on triple bond: in the presence of a phenyl group, the reaction failed and terminal acetylenes gave a different isomeric product (Scheme 187).

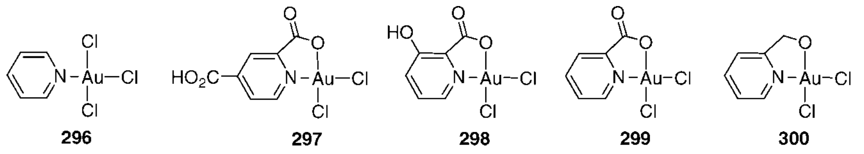
The authors proposed a mechanisms involving the π-complexation of the in situ generated cationic gold complex to the triple bond; the direct nucleophilic attack by the electron-rich phenyl ring would lead to the minor products. On the other hand, the electrophilic activation of the alkyne could trigger two successive 1,2-migrations (or a single1,3-migration) of the acetate group to produce an allene intermediate, which would be further activated by the $[Au^+]$ for hydroarylation, thus leading to main products (Scheme 188).

An efficient and atom-economical method for the synthesis of cyclic and functionalized carbo-and heterocycles has been developed by the Genêt group (Scheme 189).[289]

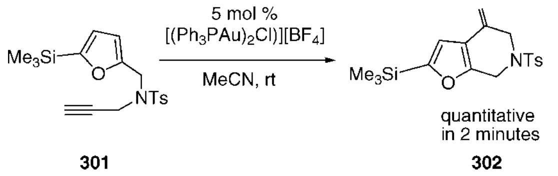
On considering the mechanism, the first generally proposed step is the formation of a cationic gold catalyst in the presence of the silver salt (Scheme 190). The complexation of the Lewis-acidic cationic gold catalyst to the alkyne function leads to intermediate **304**. The cyclization step may then occur directly through a concerted diastereoselective Friedel−Crafts-type addition/carbocyclization sequence leading to the vinylaurate intermediate **306** or may proceed by stereoselective attack of the nucleophile on a transient carbonic species **305**. The final step would be the protodemetalation of the aurate intermediate.

Indoles and pyrroles were suitable nucleophiles for the tandem Friedel−Crafts-type addition and carbocyclization reactions. It is noteworthy that the remarkable addition of the aromatic ring to the alkene is completely chemoselective. No traces of the product resulting from addition of the aromatic ring to the alkynyl moiety were detected, and the presence of the electron-rich aromatic ring completely inhibits the well documented cycloisomerization reactions. The compatibility of the $[PPh_3AuCl]/AgSbF_6$ system with various enyne substrates and its efficiency in the presence of other nucleophiles were then examined.[290] Conversely, Echavarren and co-workers reported that gold(I)-catalyzed addition of electron-rich arenes and heteroarenes to 1,6-enynes can give two different types of products by the

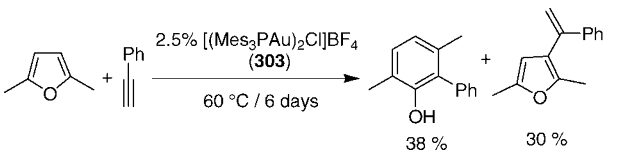
Scheme 183



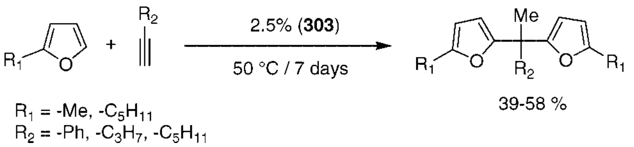
Scheme 184



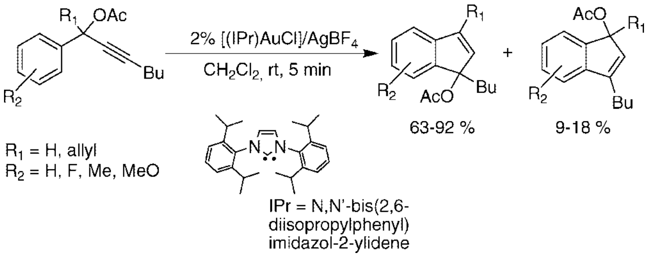
Scheme 185



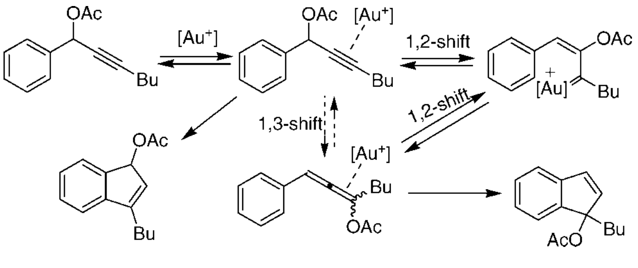
Scheme 186



Scheme 187



Scheme 188

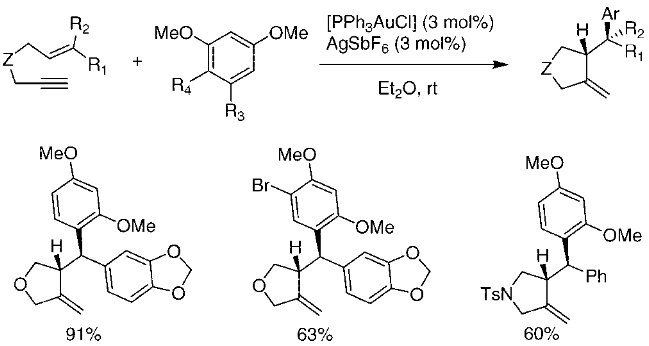


reaction of the intermediate cyclopropyl gold carbenes at the cyclopropane or at the carbene.[291]

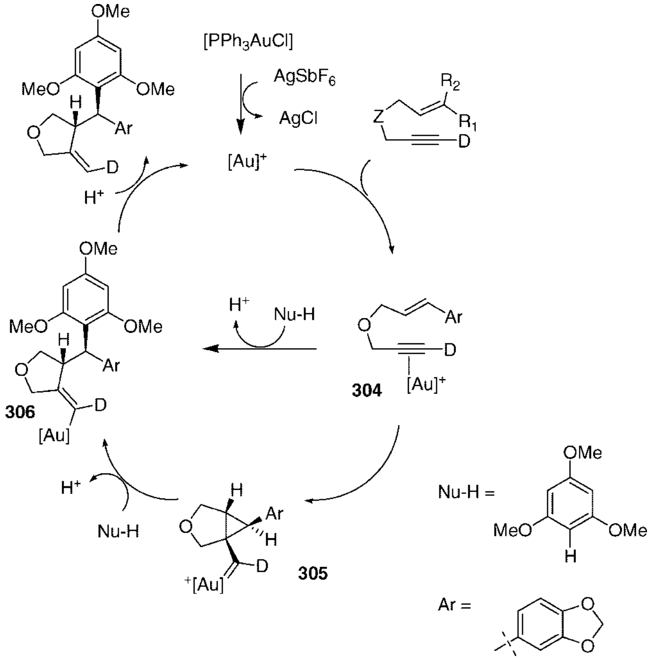
Gold-catalyzed intramolecular hydroarylation of allenic anilines **307** and phenols offers an efficient route to dihydroquinoline **308** and chromene derivatives under mild reaction conditions (Scheme 191).[292]

The hydroarylation takes place at the terminal or central allenic carbon depending on the substrate structure, leading to a highly selective formation of six-membered rings. Pd(OAc)$_2$, CuBr$_2$, and AgOTf afforded a mixture of undesired products, well as the recovered starting material. Among the catalysts investigated, gold complex **309** with AgOTf was most effective in producing the desired product.

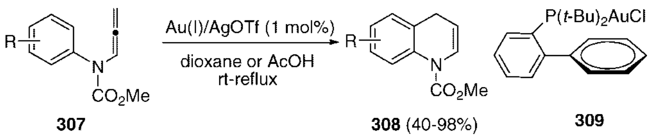
Scheme 189



Scheme 190

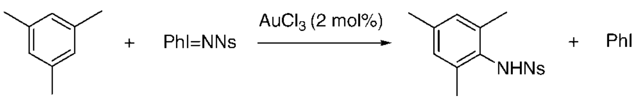


Scheme 191

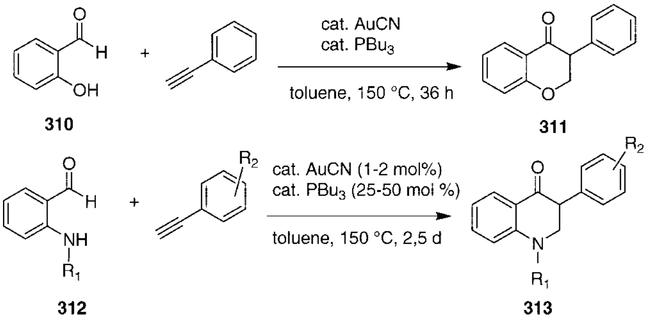


Few methods can achieve direct nitrene insertion into aromatic C−H bonds. Che et al. have utilized neighboring groups to direct a palladium-catalyzed C−N bond formation using persulfate as the oxidant, while Yu et al. reported a copper-catalyzed transformation with similar substrates.[293] In addition, Pérez et al. have reported a case of benzene amination mediated by a copper-based catalyst with the use of PhI=NTs,[294] nitrene transfer catalysts for olefin aziridination, as well as intra- and intermolecular amination of aliphatic C−H bonds.[295] However, none of these systems was successful in the intermolecular activation of aromatic C−H bonds. By contrast, gold-catalyzed nitrene insertion into aromatic and benzylic C−H bonds occurs at room

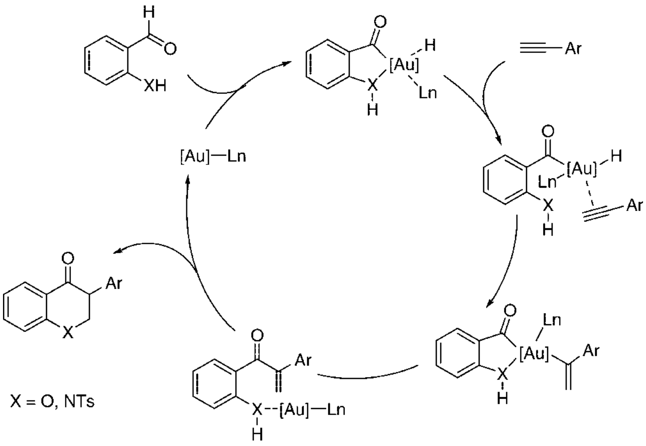
Scheme 192



Scheme 193



Scheme 194



temperature.[296] The system shows good chemoselectivity toward aromatic C−H bonds over primary and secondary benzylic C−H bonds (Scheme 192).

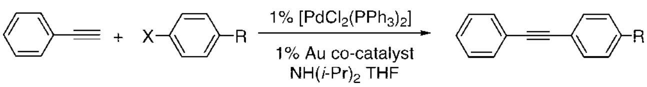
4.3. C_{sp}−H Bond Functionalization

Recetenly, Li and Skouta reported a very efficient annulation of simple 2-hydroxy arylaldehydes **310** and 2-tosylaminobenzaldehyde **312** with alkynes under gold catalysis to give isoflavanone-type[260] structures **311** and aza-isoflavone derivatives **312**, respectively (Scheme 193).[297] The 2-aminobenzaldehyde failed to give the desired product completely. It was found that the use of tosylamine greatly improved the reaction possibly because of the increased acidity of the hydrogen on nitrogen.

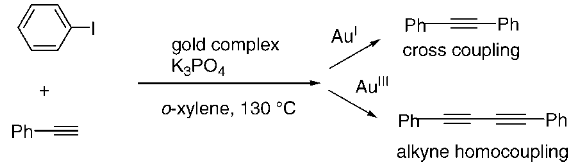
A tentative mechanism for the novel annulation has been proposed in Scheme 194. The oxidative addition of gold(I) catalyst to the aldehyde C−H bond generates an acyl gold(III) hydride. This intermediate complexes with terminal aryl alkyne, which undergoes hydrometalation. A subsequent conjugate addition of the hydroxy or tosylamino group to the α,*β*-unsaturated ketone now generated by reductive elimination gives the desired isoflavanone or aza-isoflavone derivative and regenerates the gold catalyst.

Activation of C−H of 1-alkynes by gold provided a variety of synthetic applications. A series of inorganic and organometallic compounds of gold [AuCl(tht)], [Au(C_6F_5)(tht)], and Na[$AuCl_4$] (tht = tetrahydrothiophene) are shown to efficiently cocatalyze the Sonogashira-type cross-coupling reaction of phenylacetylene with aryl halides in THF solution (Scheme 195).[298] Although reaction times are slightly longer than with CuI in THF, the use of the gold cocatalysts present the advantage of cleaner reactions, avoiding the formation of byproduct, and permits the use of technical grade solvents without previous purification or air exclusion. The compounds presented are efficient and practical cocatalysts for Sonogashira-type coupling of aryl iodides in THF and H_2O/CH_2Cl_2 biphasic systems and for activated aryl bromides in THF. The ability of the water-soluble gold complex, [AuCl(tppts)], to remain active in aqueous solution is particularly pleasing.

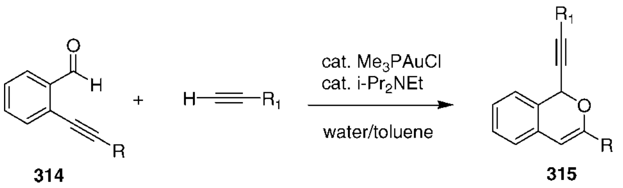
Scheme 195



Scheme 196



Scheme 197



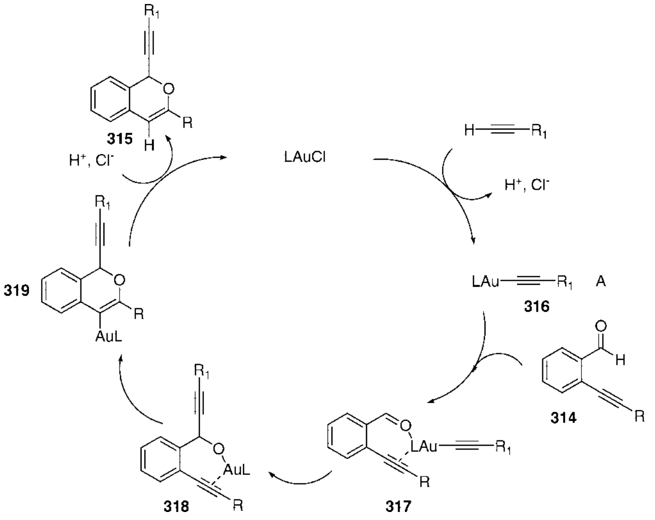
Moreover, the Corma's group showed that that Au(I), which has the same d10 electronic configuration as Pd metal and Cu(I), is active and very selective for performing the Sonogashira reaction, whereas Au(III) does catalyze the homocoupling condensation, and colloidal gold Au(0) displays low activity (Scheme 196). For comparison purposes, Pd(II) and Pd(0) complexes were also prepared and tested under the same reaction conditions. The results show that the activity of Pd catalysts is similar to that of the gold analogues.[299]

A remarkable result has been obtained by Li and Yao by reacting *o*-alkynyl benzaldehydes **314** with terminal alkynes in a mixture of water and toluene and in the presence of catalytic amounts of a tertiary base and a phosphine gold(I) complex. The reactions led to the corresponding 1-alkynyl-1H-isochromenes **315** in moderate to high yields (Scheme 197).[300]

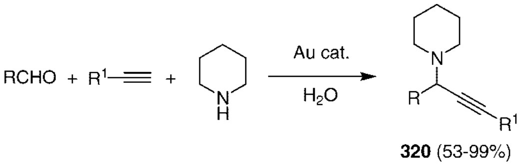
On the basis of a series of experiments and considerations, a path involving the base-promoted formation of a gold(I) acetylide species **316**, which forms a chelating intermediate **317** and activate the carbonyl group, was suggested. The acetylide then add to the aldehyde. The subsequent cyclization gave the vinylgold intermediate **319**, quenched as usual by proto-demetalation (Scheme 198).

Multicomponent approaches the molecular complexity to be increased in a single step with a clear economical and environmental gain. In this field, gold has also demonstrated this potential. The three-component coupling of an aldehyde, an alkyne, and an amine, first reported by Wei and Li is an example of this, in which the gold catalyst activate the nucleophile. The reaction gave best results in water, and even

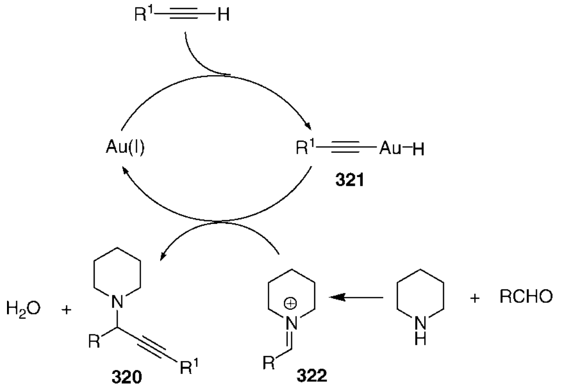
Scheme 198



Scheme 199



Scheme 200

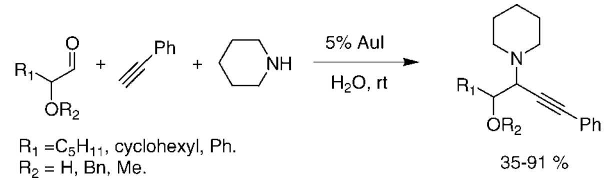


secondary diallylamine is tolerated. Both Au(I) and Au(III) salts showed excellent catalytic activities, but the Au(III) salts seemed slightly better, and the cheaper $AuBr_3$ was selected as the catalyst of choice (Scheme 199).[301]

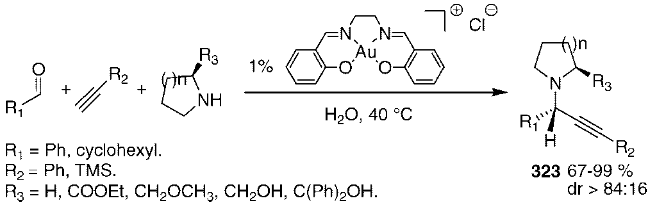
The authors proposed a mechanism involving the activation of C−H bond of alkyne by a Au(I) species generated in situ from reduction of Au(III) by the alkyne. The gold acetylide intermediate **321** reacted with the immonium ion **322** generated in situ from aldehydes and secondary amines to give the corresponding propargylamine **320** and regenerate the Au(I) catalyst for further reactions (Scheme 200)

Curiously, a nitrogen atmosphere is strictly necessary. There are several transition metal catalysts able to carry out multicomponent A^3 coupling reactions of aldehyde, alkynes and amines via C−H activation. These include Ag(I) salts,[302] Cu(I) salts,[303] iridium complexes,[304] Hg_2Cl_2[305] and a Cu/Ru[306] bimetallic system under homogeneous conditions. An A^3 coupling reaction has been reported through immobilization of Ag salts in ionic liquid,[307] Cu-supported hydroxyapatite,[308] and zinc dust,[309] although the scope is generally limited for cyclic amines. In addition, more sophisticated alternative energy sources like microwave[310] and ultrasonic[311] radiation have been used in the presence of a Cu(I) salt. However, these reagents are highly moisture sensitive and require strictly controlled reaction conditions. Reactions were carried out either in toxic solvent like toluene, in the presence of expensive solvents, such as ionic liquids, or required drastic reaction conditions. It is a considerable drawback that an expensive metal catalyst is often lost at the end of the reaction because there were no reports on the recyclability of catalyst. Metal nanoparticles are employed as a heterogeneous catalyst and could be recycled, which overcomes the serious limitation of the non-recyclability of the catalyst. Recyclable Au-nanoparticles provide an efficient, economic, novel route for multicomponent A^3 coupling reaction of aldehyde, amine and alkyne. This method provides the wide range of substrate applicability. The protocol avoids the use of heavy metals, cocatalyst and gives the propargylamine in excellent yields.[312]

Scheme 201



Scheme 202



Gold-catalyzed A^3 coupling has been extended to α-oxyaldehydes (Scheme 201).[313] On these substrates, the reaction proceed in good yields and moderate diastereoselectivity at rt. Again, both simple Au(I) and Au(III) salts are able to efficiently catalyze the transformation where Ag(I) and Cu(I) failed.

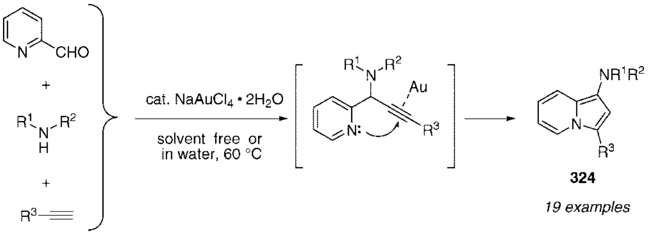
Original gold(III)−salen complexes have been used with chiral amines as substrates providing good yields and excellent diastereoselectivities. Reactions have been performed in water at 40 °C in the presence of 1% of catalyst. The strategy has been finally applied to the synthesis of propargylamine-modified Artemisine derivatives **323** (Scheme 202).[314]

More recently, Yan and Liu reported a gold-catalyzed one-step synthetic route to 1,3-disubstituted indolizines **324** under solvent-free conditions or in water, in which a gold catalyst was used as a single-pot catalyst to catalyze independent reactions in the same reaction vessel, and there was no need to isolate the intermediate of propargylic pyridines.[315] Furthermore, the coupling of optically pure (*R*)-amino acid derivatives with aldehydes and alkynes produces the corresponding indolizines without loss of enantiomeric purity. The reactions can also occurred smoothly in water at 60 °C; however, in most cases, the yields were lower than those obtained under solvent-free conditions (Scheme 203).

5. Gold-Catalyzed Selective Reductions

Recent state-of-art research in organic chemistry requires the design of highly selective transformations. In other words,

Scheme 203



only desired reactions must take place when the substrate is treated with the reagent, even if the structure of the substrate suggests numerous possibilities for reactivity. Heterogeneously catalyzed hydrogenation using gold catalysts and, in particular, those that control of the selectivity have been explored. It has been demonstrated that supported gold catalysts can show very high selectivity for the hydrogenation of substrates bearing different reducible groups, and gold has been demonstrated to have potential advantages with respect to, at first, selectivity, and then activity.[316]

5.1. Catalytic Hydrogenation of Alkenes

Mononuclear unsymmetrical N-heterocyclic carbene−gold complexes **325**−**326** and the corresponding solid catalysts in which a gold-carbene complex has been immobilized on silica gel **327-Sil**, ordered mesoporous silica **327-MCM-41**, and delaminated zeolite **327-ITQ-2** have been tested in the catalytic hydrogenation of diethyl citraconate and diethyl benzylidensuccinate at 40 °C in EtOH as the solvent and 4 atm hydrogen pressure (Scheme 204).[317] The results show that the homogeneous systems lead to quantitative conversion of olefins under the hydrogenation conditions. The better reactivity found for carbene−gold complexes compared with phosphine−gold chloride could be explained by electronic effects being more important than steric factors. The heterogenized catalysts had, in general, higher activities than the homogeneous ones. These results indicate that either the support or the metal complexes have a considerable effect on the catalytic process because of the stability of the active metallic species formed. The major advantage of the use of heterogenized metal complexes as catalysts is the ease with which they can be recovered as stable species from the reaction mixture by simple filtration and reused. Both yield and activity are retained for several consecutive experiments after the filtrate has been used in a new reaction.

Single-site homogeneous and heterogeneized gold(III) catalysts have also shown to be active for the reaction of diethyl ethylidenesuccinates (diethyl itaconate, diethyl citraconate, and diethyl benzylidenesuccinate) under mild conditions (20−70 °C and 2−6 bar H_2). It can be seen that the homogeneous gold catalysts not only are active but also give the same activity as the corresponding Pd complexes. In the case of the supported catalysts, the TOFs increase with respect to the homogeneous complex, indicating that both silica mesostructured molecular sieves (MCM-41) and delaminated zeolites (ITQ-2) are suitable supports for heterogenizing metal complex homogeneous catalysts. The mechanism of the reaction has been studied in detail by a combination of kinetic experiments and theoretical calculations. It is predicted and tested that the nature of the solvent plays a critical role for the heterolytic cleavage of H_2 (controlling step).[318] The enantioselective hydrogenation of alkenes and imines by gold(I)−Me−Duphos complexes gave also very good results.[319] In most cases, the gold catalyst reaches the activity of the platinum and iridium catalysts, and ee values clearly exceed the values obtained with the other two classical hydrogenation catalysis metals.

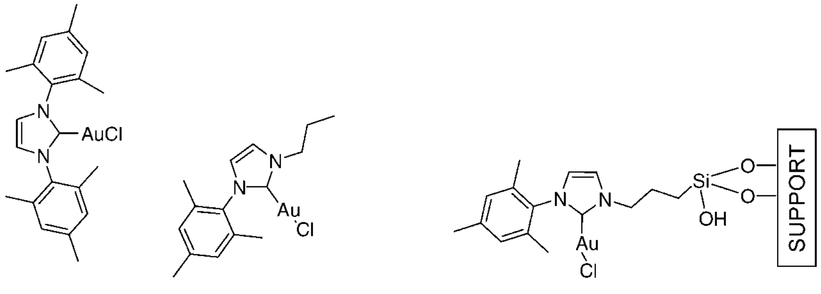
5.2. Selective Reductions of α,β-Unsaturated Carbonyl Groups and 1,3-Dienes

In reactions exhibiting a selectivity problem, for example, hydrogenation of two C═C bonds or C═C versus C═O groups, the characteristic feature of gold catalysts is the preferred hydrogenation of one of these groups leading to monoenes, unsaturated alcohols and unsaturated ketones as reaction products important to the chemical industry. The chemoselective hydrogenation of α,β-unsaturated aldehydes and ketones has attracted much interest because allylic alcohols are valuable intermediates in the production of various fine chemical, pharmaceutical, and cosmetic compounds.[320] In the intramolecular competition between saturation of the olefinic bond and the reduction of the carbonyl group, the C═C hydrogenation is thermodynamically favored. Because the kinetics of the hydrogenation strongly depend on the applied metal catalyst, the obvious challenge for catalytic chemists is to open a kinetically favored path to the allylic alcohol by the development of an appropriate hydrogenation metal catalyst. In addition, the type and degree of substitution on both the carbonyl group and the olefinic bond strongly affect the chemoselectivity of the hydrogenation. Most reports on the use of Au catalysts in the hydrogenation of α,β-unsaturated carbonyl compounds have focused on unsaturated aldehydes[321] and occasionally on the more challenging chemoselective hydrogenation of α,β-unsaturated ketones (Scheme 205).[322]

A comparative study on the selective hydrogenation of benzalacetone and cinnamaldehyde to the corresponding unsaturated alcohols on Au-supported catalysts showed that the catalytic activity and selectivity are less influenced by the morphology of gold particles and are mainly influenced by the nature of the support.[323] Very likely the active and selective sites are formed by negative gold particles formed through the electron transfer from the reduced support to the metal.

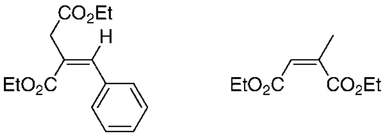
Recently, selective allylic alcohol formation has been achieved by application of Au(0) nanocolloids dispersed in amide solvents.[324] The polyvinylpyrrolidone protected Au(0) nanoparticles prefer C═O reduction over C═C saturation and act as chemoselective quasihomogeneous metal catalysts in the hydrogenation of trans-2-butenal, 2-methyl-2-propenal, 4-methyl-3-penten-2-one, and 3-methyl-3-penten-2-one. An extensive solvent screening revealed the superiority of amides as media for both synthesis and application of the Au(0) nanocolloids. In comparison with the widely used alcohol solvents, amides offer enhanced colloidal stability for the Au(0) nanosol and increased hydrogenation chemoselectivity. Control over the Au(0) cluster formation provided the opportunity to investigate the size-dependency of the catalytic performance and to determine the optimum gold cluster size for a maximization of the allylic alcohol yields. Pt(0) and Ru(0) sols are more active than the Au(0) nanosols, but substantially less chemoselective. The Au(0) nanocolloids can be recycled efficiently by ultrafiltration over custom-made cross-linked polyimide membranes. In the recycling experiments, the gold nanodispersion was well retained by the solvent-resistant ultrafiltration membranes, and the performance of the colloidal gold catalyst was satisfactorily preserved in successive hydrogenation runs. It was reported

Scheme 204



325 **326** **327-(Sil, MCM-41, ITQ-2)**

Catalytic Hydrogenation of Diethyl Citraconate and Diethyl benzylidensuccinate with Au Carbene Catalyst[a]

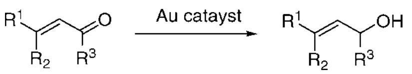


Catalyst	Conv. (%) [h]	TOF	Conv. (%) [h]	TOF[b]
(PPh$_3$)AuCl	100 [3]	25	50 [6]	6
325	97 [3]	50	55 [7]	20
326	97 [3]	225	75 [7]	75
327-Sil	100 [1]	250	90 [6]	100
327-MCM-41	100 [3]	300	95 [7]	170
327-ITQ-2	100 [2]	425	90 [6]	300

[a] Conditions: 4 atm, 40 °C.

[b] S/C ratio 500:1; TOF: mmol subs./ mmol catalyst h.

Scheme 205



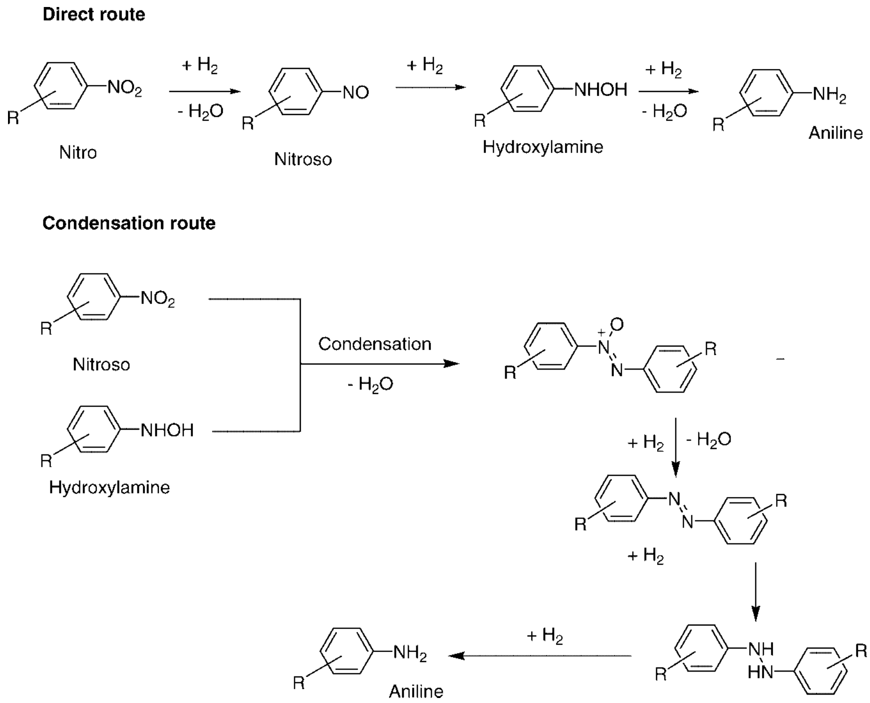
that single Au atoms/cations supported on certain oxides can catalyze hydrogenation reactions.[325] The cost of noble-metal catalysts may be decreased dramatically and homogeneous catalysis may be mimicked in a heterogeneous environment if metal cations are highly dispersed on oxides. Such a linkage between heterogeneous and homogeneous catalysis, if established, is of huge incentive.[326] Zhang et al.[325b] reported that the Au/ZrO$_2$ catalyst remains highly active at very low loadings of Au for the hydrogenation of 1,3-butadiene and that butene is selectively produced without any butane byproduct. The high selectivity is rather surprising because 1,3-butadiene hydrogenation is conventionally catalyzed by transition metals (Pd, Pt), in which the deep hydrogenation to butane is a known problem. It was suggested that Au(I) on ZrO$_2$ is the catalytically active species that can be produced from Au(III) in situ by reduction.[327] It should be realized that the prediction of Au(III) to Au(I) reduction was done using tetragonal zirconia as the model surface. High concentration of heterogenized isolated Au(III) ions at zirconia surface (55% tetragonal + 45% monoclinic) was most effective for the selective hydrogenation of 1,3-butadiene to form butenes. Copresence of metallic gold with Au(III) ions would lower the catalytic activity by TOF for 1,3-butadiene hydrogenation and change the product selectivity for more trans-2-butene and butane.[328]

5.3. Selective Reductions of Nitro Group

Corma and Serma reported the selective reduction of a nitro group in the presence of other reducible functions using gold nanoparticles supported on TiO$_2$ or Fe$_2$O$_3$.[329] In spite of the industrial importance of functionalized anilines as intermediates for fine chemicals, such as agrochemicals, pharmaceuticals, and dyestuffs, there are only few generally applicable catalytic systems for the selective reduction of a nitro group in the presence of C═C, C≡C, C═O, C≡N, C'N, or groups. The use of older stoichiometric reducing agents is not environmentally sustainable. The reduction to anilines occurs in several steps, either by the direct route via nitroso and hydroxylamine intermediates or via a condensation route; the latter route is favored under basic conditions (Scheme 206). The slowness of the reduction step involving the hydroxylamine intermediate can represent an additional problem because its accumulation determines the formation of unwanted byproduct and possible runaway reactions because of decomposition (with accompanying health and safety issues).

The key aspect of the alternative gold-catalyzed procedure for the chemoselective reduction of nitro groups is that very little byproduct is observed, and they have presented a

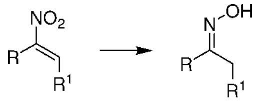
Scheme 206



substantial problem and challenge for researchers who previously focused on the use of supported Pt catalysts. Two supported gold catalysts [1.5 wt % (wt %) Au/TiO2 and 4.5 wt % Au/Fe_2O_3], as well as Pt-, Pd-, Au−Pt-, and Au−Pd-supported catalysts were used for the hydrogenation of 3-nitrostyrene with H_2 under mild reaction conditions (9 bar, 120 °C). The results (Table 1) show that the Pt, Pd, Au−Pd, and Au−Pt catalysts were not selective for this reaction. However, the two supported gold catalysts gave conversions >98% with 96% selectivity to 3-vinylaniline, whereas the residual product was 3-ethylaniline. The evolution of the reaction products when Au/TiO_2 and Au/Fe_2O_3 are used as catalysts for the hydrogenation of 3-nitrostyrene shows only traces of hydroxylamine styrene, azostyrene, and azoxystyrene. Results show that hydroxylamines derivatives are also avoided for multiple turnovers of the catalyst. Therefore, if the aryl hydroxylamine can be formed on the gold catalysts, it apparently reacts rapidly to give the corresponding aniline.

The chemoselective reduction of the nitro group in the presence of a carbonyl, nitrile, and amide groups has been also studied. In all cases, the selectivity was still higher in the case of gold catalysts. Given the excellent chemoselectivity of gold for reducing nitro compounds, the Corma's reseach group also explored gold catalysis as an alternative catalytic route for the production of oximes by hydrogenation of α,*β*-unsaturated nitrocompounds with H_2. Traditionally, oximes are synthesized by condensation of an aldehyde or a ketone with hydroxylamine, but the use of this reagent is less desirable for large scale processes because of its intrinsic toxicity and unstability. Other functional group transformations and, particularly, partial reduction and isomerization of the nitro groups, require harsh reaction conditions and are characterized by poor selectivity. The hydrogenation of α,*β*-unsaturated nitrocompounds **328** to produce oximes is not trivial because of the presence of the easily reducible double bond, as well as the possibility of undesired secondary reactions in molecules with sensitive groups (Scheme 207).

Scheme 207



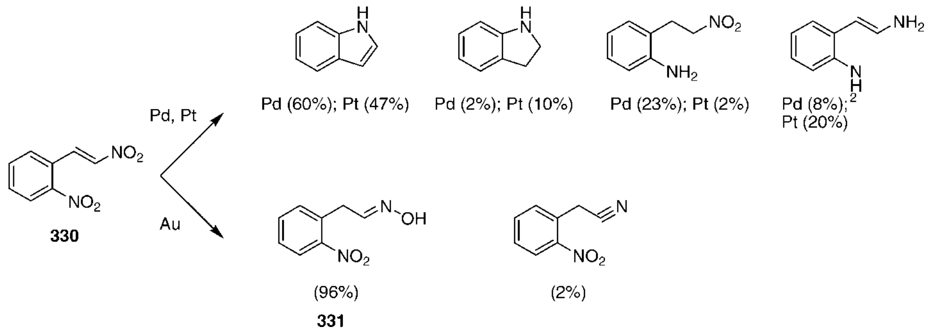
328 **329**

According to traditional methodologies, the only possibility in achieving certain selectivity of the oxime, when reacting α,*β*-unsaturated nitrocompounds, was the use of stoichiometric amounts of organic hydrogen donors (e.g., ammonium formate, decaborane, formic acid, etc).[330] However, the use of these organic or inorganic reductants is not industrially sustainable from an environmental point. The use of gold on TiO_2 as catalyst has allowed the establishment of an alternative method for obtaining oximes from α,*β*-unsaturated nitrocompounds with H_2.[331] The reaction is considerably greener than any of the known alternatives and involves an easy work up. Gold, unlike other noble metal-based catalysts, such as commercial Pd/C or Pt/C, shows a unique selectivity. When a second nitro group is present in the reactant molecule (*β*,2-dinitrostyrene **330**), results show large differences between the catalytic behavior of Pd and Pt with respect to

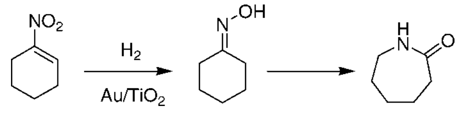
Table 1. Catalytic Results of the Chemoselective Hydrogenation of 3-Nitrostyrene

catalyst	% metal (mol)	*T* (°C)	*P* (bar)	time (h)	conversion (%)	selectivity (%)
Au/TiO_2	0.23	120	9	6.00	98.5	95.9
Au/Fe_2O_3	0.39	130	12	9.50	95.2	95.1
Pd/C	0.11	120	9	0.03	99.0	0.0
Pt/C	0.12	120	9	0.03	96.7	2.9
Au−Pd/TiO_2	0.20	120	9	0.03	99.5	0.0
Au−Pt/TiO_2	0.31	120	9	0.02	93.0	1.8

Scheme 208



Scheme 209



Au/TiO_2. Neither the Pd nor the Pt catalysts are able to produce the aromatic oxime **331** owing to the occurrence of other competing reactions, such as hydrogenation of the double bond, reduction of one or both nitro groups to anilines, and reductive cyclizations. Indole has been found as the main byproduct (60% and 47% with Pd and Pt, respectively). On the contrary, the Au/TiO_2 catalyst is remarkably selective toward the oxime formation, and the reduction of the aromatic nitro group to the corresponding aniline is totally avoided (Scheme 208).

Finally, the procedure is shown to be applicable also to nonaromatic unsaturated nitro compounds, such as 1-nitro-1-cyclohexene. The reaction with the Au/TiO_2 catalyst allows one to obtain the industrially relevant cyclohexanone oxime, an important intermediate in the production of ε-caprolactame, in excellent yields accomplishing the development of an alternative route for its production (Scheme 209). The gold-catalyzed process should open the possibility to avoid the use of hydroxylamine, which is a toxic and unstable product.

A different reaction pathway for the reduction of aromatic nitro compounds on gold catalysts has been shown by combining in situ IR spectroscopy with macrokinetic experiments. These studies allowed the determination of reaction intermediates and relative elementary steps during gold catalysis.[332] The aromatic nitro compounds are hydrogenated on Au/TiO_2 by the reaction route shown in Scheme 210. This reaction pathway differs from that reported for $Pt/CaCO_3$ and $Pt/C-H_3PO_4$ and explains why the presence of iron or vanadium salts is not required for the reaction with the gold catalyst to proceed with high selectivity for the aniline products. The results indicate that that it is possible to reduce nitrobenzene to phenylhydroxylamine directly. Then, on Au/TiO_2 catalysts, phenylhydroxylamine is formed as both a primary product and a secondary product at the Au/TiO_2 active sites. The gradual accumulation of this intermediate on the catalyst surface shows that the transformation of phenylhydroxylamine into aniline is the rate-determining step of the whole process. Furthermore, the fact that only very small amounts of azoxybenzene were observed in the liquid phase batch experiments suggests strongly that the inhibition of the condensation of hydroxylamine and nitroso intermediates during the hydrogenation of aromatic nitro compounds on Au/TiO_2 catalysts is predominantly a result of the low concentration of nitrosobenzene.

6. Oxidation Reactions

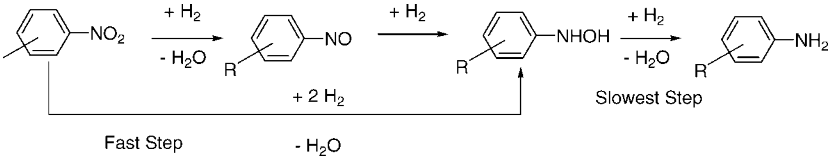
The replacement of conventional stoichiometric oxidations by environment-friendly catalytic processes is currently a widely accepted strategy in fine chemicals industry. Hence, the area of elaborating new catalytic technologies for the selective oxidation of complex and thermally sensitive molecules is advancing rapidly. Many efforts are aimed at eliminating waste, maximizing the incorporation of raw materials into the final product, avoiding, where possible, the use of auxiliary substances including solvents, and employing (recyclable) catalysts. Moreover, the demand for greener, more atom-efficient methods involves the employment of clean oxidants such as O_2 and H_2O_2. Selectivity is a general problem in both stoichiometric and catalytic strictly O_2-based oxidations because these reactions are nearly always dominated by radical chain autoxidation, a chemistry that is intrinsically nonselective and difficult to control. Gold has received a growing interest as a catalyst for the selective oxidation of organic molecules by these clean oxidants under mild conditions.[333] The recent developments in this emerging field of catalysis by gold are summarized as follows.

6.1. Epoxidation and Aziridination Reactions

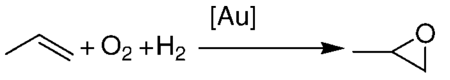
The development of an efficient catalyst for the production of propene oxide, a very important intermediate for the synthesis of commercial products is a challenging task. The current methods used for propene oxide synthesis have important disadvantages. The chlorhydrin process involves the production of chlorinated side products and calcium chloride waste, whereas the hydroperoxide process produces a stoichiometric amount of coproduct.[334] The surprisingly high catalytic activity of gold in the direct epoxidation of propene with hydrogen and oxygen (Scheme 211) indicates that they may be commercially viable for propene epoxidation.[335]

The details of the current understanding of the features of gold catalysts for propene oxidation have recently been reviewed.[336] Fundamental aspects obtained from surface science studies and the utility of metastable oxygen species on Au catalysts by selecting appropriate reaction conditions that kinetically control the state of surface have been highlighted.[337] Theoretical study has been undertaken to shed light in the interaction between O_2 and H_2O and the Au cluster as a first step for understanding the catalytic activity of Au catalysts in the presence of moisture. Hybrid density functional theory calculations have been mainly carried out on the charge transfer interaction between Au and oxygen or H_2O in Au model clusters.[338] In part because of the complexity of the reaction system, there are still many unanswered questions as to how to efficiently promote

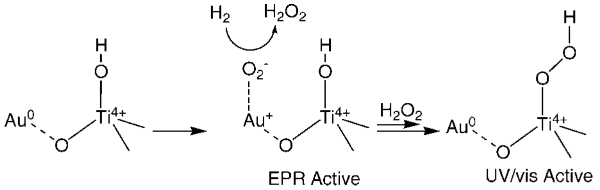
Scheme 210



Scheme 211



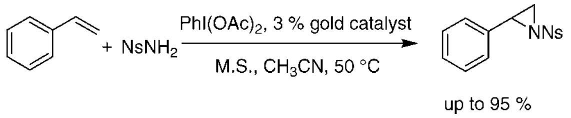
Scheme 212



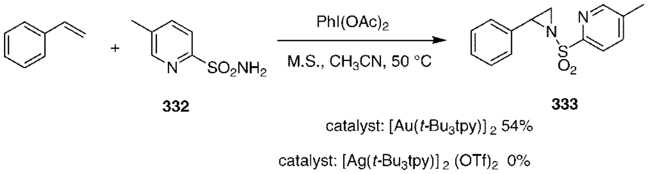
epoxidation using Au-based nanocatalysts. It is well-known that both the electronic state and the structure of Au clusters are dramatically changed depending on which support is selected. Modified electronic structure of Au nanoclusters has been suggested to the formation of activated Au−O complexes.[339] Moreover, even if the support used is the same, the characteristics of the Au clusters deposited could be different depending on the surface condition, such as reduced and oxidized surfaces of the support. Catalysts consisting of gold nanoparticles on titania supports have received considerable attention. The viability of the vapor-phase epoxidation of propene over Au nanoparticles supported on Ti-based oxides such as TiO_2, TiO_2−SiO_2, TS-1, Ti-MCM-41, Ti-MCM-48, Ti-containing hydrophobic silsequioxanes and three-dimensional mesoporous titanosilicates has been demonstrated. Hydroperoxide species have been postulated as an intermediate responsible for the epoxidation reaction. To obtain direct evidence for the different type of active oxygen species, in situ UV−vis and EPR measurements were carried out during the epoxidation of propene with O_2 and H_2 over a Au/Ti−SiO_2 (Ti/Si = 3:100) catalyst (Scheme 212).[340]

It was determined that the adsorbed species of oxygen (O_2^-) resided on Au, more likely at a perimeter site, and it led to the formation of titanium hydroperoxo species. These results support the possible mechanism of formation of these hydroperoxo species via H_2O_2 produced from O_2 and H_2 adsorbed on the Au surfaces. Gold can activate oxygen and hydrogen to form H_2O_2 via formation of an intermediate (O_2^-) paramagnetic species on the gold surface. Hydroperoxo species can then be formed by transfer of H_2O_2 to Ti^{4+} sites. This hydroperoxo species on the tetrahedrally coordinated Ti cation sites can then react with propene adsorbed on SiO_2 surfaces to form propene oxide (PO). The UV active Ti−hydroperoxo species and the EPR active (O_2^-) species could be directly detected. The appearance of both species in appreciable amounts when gold is present highlights the vital role of gold nanoparticles on Ti−hydroperoxo species formation, which are indispensable for the production of PO from propene. The presence of trimethylamine (TMA) at extremely low concentrations (10−20 ppm) in the reactant gas mixture can remarkably improve the catalytic performance of gold nanoparticles deposited on titanosilicate in terms of catalyst lifetime, catalyst regeneration, PO selectivity, and H_2 efficiency.[341] In the process, hydrogen and oxygen react to form H_2O_2 and H_2O over the Au surfaces; thus the H_2 efficiency is usually below 100%. Once the H_2O_2 is produced on the gold particles, it can be converted into hydroperoxo species at tetrahedrally coordinated Ti cation sites. These Ti−hydroperoxo species can subsequently react with propylene adsorbed on the SiO_2 surfaces to form PO. Because of its basic properties, PO should compete strongly with TMA to adsorb on the catalyst surface. Preadsorption of TMA on Ti^{4+} can therefore inhibit PO adsorption and its subsequent oligomerization, which is considered to be one of the main deactivation mechanisms of Au/titanosilicate catalysts. The efficient regeneration of the Au/titanosilicate catalyst using a trace amount of TMA, along with a mixture of hydrogen, oxygen, and argon, at 523 K, and the improvement of the hydrogen efficiency to 35%, opens the door to commercialization of this catalytic process. This economic synthetic method is an example of a chemical process that can meet industrial standards while being environmentally benign. Kinetic results consistent with a mechanism involving the production of hydrogen peroxide on gold and the propene oxide on titanium centers have been reported for gold catalyst supported on the mesoporous titanium silicate, Ti-TUD.[342] Information from catalytic experiments and a detailed infrared study indicates that the formation of a bidentate propoxy intermediate can led to deactivation of the catalyst through further oxidation to strongly adsorbed carboxylate species.[343] Deactivation of the Au catalyst occurs to lesser extent when TiO_2 was incorporated into SiO_2 or other modified supports. Ti−Si mixed oxides prepared from chloride precursors using a one-step nonhydrolytic sol−gel route could serve as efficient gold catalyst support for gas-phase epoxidation of propene.[344] Sylilation of Au catalysts supported on disordered titanosilicates has been found to have a very positive influence in PO yield.[345] Furthermore, the Au/titanosilicate catalyst activity can be enhanced by addition of $Ba(NO_3)_2$ as a promoter. Elemental analysis showed that Ba increases the amount of gold retained by the catalyst.[346] Highly dispersed gold nanoparticles were synthesized within the channels of a mesoporous Ti-SBA-15 support. For this purpose, two series of Ti-SBA-15 materials differing in their Ti content were prepared by either grafting or direct synthesis. The reaction data indicate that Au/Ti-SBA-15 materials obtained by Ti grafting have greater catalytic activity than the samples in which Ti-SBA-15 was obtained by direct synthesis. These differences in catalytic behavior are attributed to differences in the amount and dispersion of Ti within the mesoporous silica support, as well as to differences in the Au nanoparticle size.[347] The potential for Au/C as a selective oxidation catalyst has been explored.[348] The findings suggest that the Au/C catalysts are tunable by careful selection of the reaction conditions to epoxidize alkenes avoiding sacrificial reductant.[349] Small amounts of either hydrogen peroxide or *tert*-buthylhydroperoxide are needed as oxygen chain initiators. The formation of the corresponding epoxide from a variety of alkenes resulted dependent on the type of solvent used, even if good

Scheme 213



Scheme 214



332

333

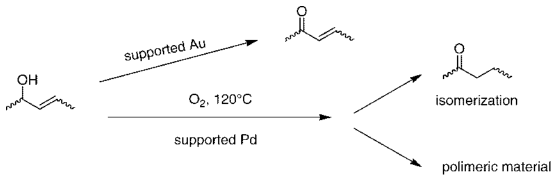
selectivities have been observed under solvent-free conditions. Chlorine significantly enhances the selectivity of styrene epoxidation on Au(111) by inhibition of secondary oxidation, especially combustion and the deposition of residual carbon. There was no measurable decrease in the rate of styrene epoxidation during five consecutive reaction cycles of oxidation by O_3 and reaction of styrene on chlorine-covered Au(111) at 300 K. The effect of Cl persists over several turnovers.[350]

Metal-catalyzed nitrene transfers to unsaturated and saturated organic substrates are important tools in synthetic chemistry.[351] Various transition metal complexes have been shown to catalyze these transformations.[352] Disilver(I)-based catalyst, with 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″terpyridine (*t*-Bu$_3$tpy) as the ligand, mediated efficient olefin aziridination and intramolecular amidation of saturated C−H groups.[353] This success prompted the exploration of nitrene-transfer reactions that could be catalyzed by similar complexes of the other two coinage metals, gold and copper. Indeed, a gold(I) compound, supported *t*-Bu$_3$tpy as the ligand, efficiently catalyzes olefin aziridination with the use of the commercially available oxidant $PhI(OAc)_2$ and sulfonamides (Scheme 213).[354]

The process avoids the use of the sulfonyliminoiodinane-type nitrenoids, which are commonly employed in olefin aziridination reactions and have to be synthesized beforehand in unsatisfying yields. *p*-Nitrosulfonamide ($NsNH_2$) was employed to react with different olefins. The use of styrenes bearing different functional groups led to excellent yields of the corresponding aziridines, but the aziridination of simple aliphatic olefins could not be mediated by gold catalyst, except for activated ones and intramolecular reactions. Other types of sulfonamides can be employed, albeit with lower product yields in some cases. It should be noted that the reactions with 5-methylpyridine-2-sulfonamide **332** as the nitrene sources did not work for the disilver(I)-based catalytic system, which indicates reactivity difference between the two systems (Scheme 214).

The aziridation of a C=C bond by using a heterogeneous gold system, which may provide a convenient and more efficient route has been investigated.[355] Aziridation of styrene does occur on Au(111) covered with NH_x. The results indicate that 2-phenylaziridine is formed from the Au-promoted reaction of styrene and NH_x. In the reaction, oxygen is used to activate the NH_3 and to form NH_x species on the surface. By adjustment of the preparation condtions, oxygen is consumed by the NH_3 and forms H_2O, wich desorbs, and NH_x, remains on the Au(111) surface.

Scheme 215



6.2. Selective Oxidations of Alcohols

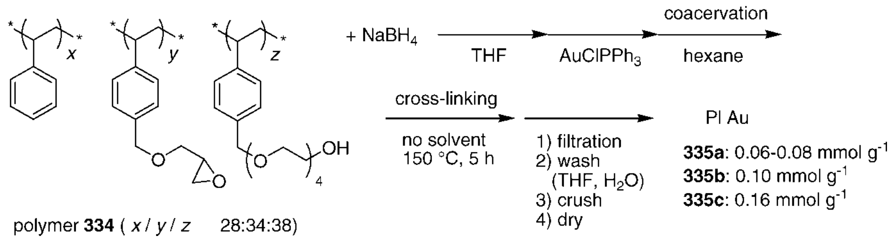
Selective oxidation of alcohols to carbonyl compounds is one of the most critical challenges facing the chemical industry.[356] Traditionally, the oxidation of alcohols has been achieved with stochiometric inorganic oxidants as Cr(VI)-based reagents. Although these reagents are quite general in scope, they are no longer tolerable from a green chemistry point of view. Ever-increasing environmental concerns has resulted in much attention being recently directed toward the development of new protocols for aerobic oxidation of alcohols using transition-metal catalysts.[357] Because of recently developed or improved synthesis methods, gold metal particles can be generated as nanoclusters.[358] Gold nanoparticles supported on cerium oxide,[359] other inorganic oxides,[360] active carbon,[361] or even unsupported gold nanoparticles[362] have recently attracted considerable attention because these catalysts are able to promote the selective oxidation of alcohols. More recently it has been presented the benefit of using nanoparticulated CeO_2 instead of the conventional ceria as a support for gold nanoparticles resulting in a highly active, selective, and recyclable catalyst for the oxidation of alcohols into aldehydes and ketones using oxygen at atmospheric pressure as oxidant in the absence of solvent and base.[363] High turnover frequencies for the oxidation of selected alcohols with oxygen under mild condition have been achieved using titania-supported gold (core)−palladium (shell) nanoparticles.[364] An air- and moisture-stable oxidation catalyst, to be useful for organic chemists, has to give not only high conversion with some selected alcohols but also has to be chemoselective when the molecule contains other oxidizable functional groups. In this case, one important family of alcohols that has industrial relevance are allylic alcohols. In this common type of alcohol chemoselective oxidation of hydroxyl groups avoiding oxidation, isomerization or polymerization of the olefinic group is required. Corma and co-workers showed that for the relevant oxidation of allylic alcohols, gold presents unique selectivity[365] when compared with Pd or Au−Pd catalysts (Scheme 215).

Catalytic data highlighted that gold nanoparticles (3−7 nm) supported on nanoparticulated ceria (4 nm) are far more chemoselective than related palladium catalysts for the aerobic oxidation of allylic alcohols.[366] Most likely the lower tendency of gold nanoparticles to form reactive hydrides as compared to palladium catalysts is beneficial for both undesired processes, i.e. isomerization and hydrogenation. The reusability of the Au−CeO_2 catalyst has been checked. The solid was recovered by filtration, washed with a 1 M aqueous solution of NaOH, and dried in vacuum. The recovered Au−CeO_2 sample was used in a consecutive run without observing any decay in its catalytic activity. The presence of palladium in the catalyst resulted highly detrimental for chemoselectivity. The effect of the Au−Pd ratio on the catalyst performance, and in particular on the formation of nonselective reaction products has been also explored.[367] Chlorine-free benzaldehyde can be produced by an environmentally friendly solvent-free liquid phase oxidation of benzyl alcohol with molecular oxygen, even at low pressure (1.5 atm), using nanogold-supported U_3O_8, particularly prepared by the homogeneous deposition precipitation method.[368] The Au/U_3O_8 is a highly promising, easily separable, and reusable catalyst for the solvent-free selective oxidation process. There is an optimum catalyst calcination temperature (400 °C) for achieving the highest benzyl alcohol conversion and benzaldehyde selectivity. The better process performance (i.e., higher benzaldehyde yield and selectivity) is achieved when the catalyst contains gold at higher concentration and also with smaller particle size. With increasing reaction period or temperature, the benzyl alcohol conversion is increased markedly, but there is a small decrease in the selectivity for benzaldehyde and a small increase in the formation of benzyl benzoate. In the presence of commonly used solvent (toluene, *p*-xylene, dimethyl formamide, or dimethyl sulfoxide), the process performance (both the benzaldehyde yield and selectivity) is found to be inferior to that observed in the absence of any solvent. The Au/U_3O_8 is also a highly promising catalyst for the solvent-free oxidation of substituted benzyl alcohols by O_2 to corresponding aldehydes or esters with good selectivity and yields. Through proper choice of the functional monomer (vinylpyridine), Au nanoclusters of small size and with a narrow size distribution can be generated. The resulting microgel-stabilized Au nanoclusters have been shown to be remarkably active "quasi-homogeneous" catalysts for the aerobic oxidation of primary and secondary alcohols in water.[369] Solvent-free oxidation of benzyl alcohol was investigated in the absence of a base using Au catalysts prepared by sol immobilization on titania and carbon supports. Sol immobilization is a suitable technique for preparation of gold catalysts with small particle size, narrow particle size distributions, and very high activity and selectivity for benzyl alcohol oxidation.[370] The oxidation of benzyl alcohol with molecular oxygen under solvent-free conditions has been also investigated using a range of titania-supported Au−Pd alloy catalysts.[371] The catalysts have been compared at high reaction temperature (160 °C), as well as at 100 °C, to determine the effect on selectivity because at lower reaction temperature the range of byproducts that are formed are limited. Under these conditions the 2.5 wt.% Au-2.5 wt.% Pd/TiO_2 was found to be the most active catalyst, whereas the Au/TiO_2catalyst demonstrated the highest selectivity to benzaldehyde. Toluene is formed in the mixed $Au-Pd/TiO_2$ catalysts even at very low conversions and at short reaction times, indicating it is possibly a primary reaction product. Binary and ternary mixed oxides containing Mg−Al, Cu−Al, and Cu−Mg−Al prepared by flame spray pyrolysis (FSP) resulted in agglomerated primary nanoparticles in the 10−15 nm range, onto which 6- to 9-nm gold particles were deposited by means of deposition−precipitation. These mixed-oxide-supported Au catalysts with noble metal loading of 0.6 ± 0.17 wt % were tested in the aerobic liquid-phase oxidation of 1-phenylethanol to phenyl-methyl ketone affording TOFs up to 1300 h^{-1}. The catalytic tests showed that the activity of these catalysts depends strongly on the composition of the support, with Cu and Mg being crucial components. Strongly enhanced catalytic activity was observed for gold supported on a ternary mixed oxide containing Cu, Mg, and Al at the molar ratio of 5:1:2. Extension of the catalytic tests to various structurally different alcohols indicated that the ternary mixed-oxide-supported gold catalyst has excellent catalytic properties in the aerobic oxidation of a broad range of structurally different alcohols, affording selectivities 98%. XANES revealed both reduced and oxidized Au species on the ternary mixed-oxide supports before and after the reaction. Mesoporous silica materials (GMS) with nanoscale-gold in the framework were prepared by functionalizing the silica with thioether groups. Characterization of the materials demonstrated that they possess unusually high surface area and pore volume, the pore size distributions were very narrow, and there were large amounts of void defects in the pore walls. These materials were evaluated for the solvent-free liquid phase aerobic oxidation of benzyl alcohol by molecular oxygen. Benzaldehyde was obtained with high selectivity under the reaction conditions of 403 K, 15 atm, and 5 h. The 1.5% GMS catalyst was also very active for atmospheric pressure aerobic oxidation of benzyl alcohol and was stable under the reaction conditions, and the conversion was still better than 99% after recycling three times.[372] Moreover, the oxidation of benzyl alcohol to benzaldehyde has been investigated over different supported gold catalysts in supercritical carbon dioxide in a high-pressure batch reactor.[373] Only molecular oxygen was used as oxidant, and no base was needed. Different supports and preparation methods for the catalysts were tested, and parameters, such as reaction temperature, pressure and molar ratios of the components, were varied to study the catalytic behavior. Gold colloids deposited on a titania support (1%Au/TiO_2) yielded a conversion of 16.0% after 3 h and a high selectivity to benzaldehyde of 99% under single-phase conditions. The reaction rate was significantly higher than in a corresponding "solvent-free" reaction without CO_2. Even higher rates were found when a CO_2-expanded phase was present. Monitoring of the oxidation in a high-pressure view cell via infrared transmission spectroscopy unravelled a slowdown of the reaction rate above 15% conversion. In addition, 1-octanol and geraniol were oxidized as well under similar conditions, yielding conversions of 4% and 10%, respectively, with selectivities toward octanal and geranial of 90% and 30%. Thus, the combined application of gold-based catalysts and supercritical CO_2 offers an interesting alternative to the known methods of alcohol oxidation.

It is known that aromatic molecules such as benzene can interact weakly with gold surfaces or gold nanoclusters through the π-electrons of benzene rings.[374] Therefore, it was reasoned that if the gold nanoclusters could be stabilized by weak interactions with the aromatic sections of polymers, they might be versatile catalysts that could be used for liquid-phase organic synthesis with a more wide range of substrates. A size-controllable gold nanocluster catalyst, polymer-incarcerated gold (PI Au) **335**, which used multiple interactions with the benzene rings of polymer **334** has been prepared (Scheme 216) and the selective aerobic oxidation of alcohols catalyzed by PI Au **335** under air or oxygen atmosphere at room temperature is also reported.[375]

PI Au nanoclusters **335** thus prepared were used for the aerobic oxidation of (±)-1-phenylethanol. The reaction proceeded in a dichloromethane/water solvent mixture at room temperature and under oxygen at atmospheric conditions in the presence of **335a** (3 mol %) and potassium carbonate to afford acetophenone quantitatively. The reaction also proceeded smoothly in toluene/water and benzotrifluoride (BTF)/water solvent mixtures. It is notable that, in all cases, no metal leaching was detected by inductively coupled plasma (ICP) analysis (<0.04%). Examination of the rela-

Scheme 216



Scheme 217

$$\mathbf{334} + NaBH_4 \xrightarrow[\text{diglyme}]{} \xrightarrow[AuClPPh_3]{} \xrightarrow[Et_2O]{\text{coacervation}}$$

$$\xrightarrow[\substack{\text{no solvent}\\ 150°C,\ 5h}]{\text{cross-linking}} \xrightarrow[\substack{\text{1) filtration}\\ \text{2) wash}\\ (CH_2Cl_2,\ H_2O)\\ \text{3) crush}\\ \text{4) dry}}]{} \xrightarrow[\substack{\text{no solvent}\\ 150°C,\ 5h}]{} \mathbf{336}\ \substack{0.06\text{-}0.08\\ mmol\ g^{-1}}$$

tionship between the reactivities and the loadings of the gold catalysts revealed that use of a lower loading gave higher activity, which could be rationalized by the fact that a lower catalyst loading contained smaller clusters. Furthermore, it was found that a slight modification of the preparation method of the PI Au nanoclusters greatly increased their catalytic activity (Scheme 217).

It was proved that the reaction was promoted by a base and that the reaction did not proceed at all in the absence of water or base. The catalyst was recovered by simple filtration and reused without significant loss of activity (Scheme 218).

The recovered catalyst could be heated at 150 °C for 5 h to facilitate its reuse. Several alcohols were then oxidized in an oxygen or air atmosphere in the presence of 1−3 mol% of **336**. Aromatic secondary alcohols were oxidized smoothly to afford the corresponding ketones quantitatively. Aromatic and allylic primary alcohols were oxidized smoothly in the presence of a weak base to afford the corresponding aldehydes in good yields, although the products were accompanied by small amounts of carboxylic acids or esters. Alcohols that contained heteroatoms such as S and N, which are well-known to coordinate strongly to gold nanoparticles, could be oxidized smoothly to give the desired ketones in high yields without leaching of the metal.

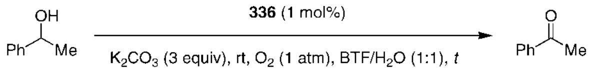
A persistent problem in the practical use of finely dispersed gold nanoclusters (AuNCs) is their aggregation, especially during reactions and/or workup procedures. A stable micelle structure would be used as a scaffold to prevent aggregation of these species. A star polymer consisting of many hydrophilic arms and a hydrophobic core can be regarded as a unimolecular micelle. Recently, Aoshima et al. achieved a significant advance in star polymer synthesis, demonstrating quantitative formation of vinyl ether star polymers with low polydispersity.[376] In addition, it has been found that polyvinyl ethers with oxyethylene side chains exhibit LCST (lower critical solution temperature)-type phase-separation behavior in water. Therefore, they examined the preparation of AuNCs **338** in water using star polymers consisting of 2-(2-ethoxy)ethoxyethyl vinyl ether (EOEOVE) **341**, as illustrated in Scheme 219. The resulting clusters were shown to catalyze aerobic oxidation under mild conditions without deterioration.[377] Furthermore, the catalyst could be recovered for reuse via simple procedures using thermosensitivity of the arm chains.

AuNCs **341** catalyze the oxidation of benzyl alcohol in water under aerobic and mild conditions to afford the corresponding acid (benzoic acid) in almost quantitative yield (Scheme 220). In addition, **341** induced several aerobic oxidation reactions of benzyl alcohol derivatives into the corresponding carboxylic acids (*p*-nitrobenzyl alcohol, 89% under similar conditions). Moreover, the AuNCs were able to catalyze oxidation from an primary alcohol to the corresponding carboxylic acid. In all cases, oxidation reactions proceeded under milder conditions, compared to previous studies. It should be noted that the AuNCs did not undergo negative aggregation at any point during the reaction or even during workup procedures, which was confirmed using the TEM method.

The homogeneous oxidation of alcohols catalyzed by gold has more rarely been reported. Gold(I) chloride plus *β*-diketiminate anion **342** as ligand serves as an excellent catalyst for highly selective aerobic oxidation of alcohol.[378] The ligand bears a negative charge and is quite donating; the flanking 2,6-diisopropylphenyl group on the nitrogen atoms provide steric hindrance to leave open coordination sites on the center metal ion to bind an oxygen transfer reagent and perhaps also substrates to facilitate the oxidation process. Benzyl alcohol has been oxidized to benzaldehyde in 99% GC yield with 100% conversion in toluene at 90 °C after 10 h with O_2 as the oxidant (Scheme 221). The use of 4 Å molecular sieves is beneficial the reaction. Further study indicated that the oxidation also ran smoothly under air atmosphere. Then the scope of the method was illustrated with a range of alcohols. With the use of activated primary benzyl and allylic alcohols, both conversions and yields were very high with excellent selectivity; only aldehydes were produced under the reaction conditions with no overoxidized carboxylic acid observed.

Some alcohols could also be oxidized to carbonyl compounds with a 1:1 ratio of gold(I)-neocuproine **344** as a catalyst in aqueous solution (Scheme 222).[379] Remarkably, the aerobic oxidation ran very smoothly when the pressure of oxygen was increased to 50 atm in the presence of 1 M $NaHCO_3$. Surprisingly, the oxidation could not run very efficiently in the presence of NaOH (1.0 mol/L) under 50 atm of O_2. Organic base, such as Et_3N, was very inefficient. $AuCl_3$/**344** could also catalyze this oxidation but the efficiency of this reaction was much lower. Similarly, the oxidation could not perform well under 50 atm of O_2 in the absence of either AuCl or any ligand in water. The increase of steric hindrance can also observably decrease the efficiency of oxidation. Primary mechanistic studies showed that the rate of oxidation was related to the pressure of O_2 and the pH value of the solution. The results also indicated that this catalytic process was mechanistically different from those catalyzed by solid-supported gold nanoparticles, and gold complexes were assumed to be catalytic species in solution.

Scheme 218

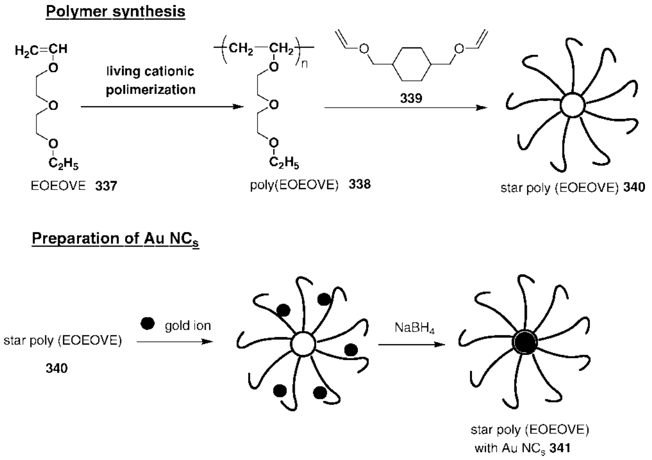


Entry	*t* [h]	Use						
		1st [%]	2nd [%]	3rd [%]	4th [%]	5th [%]	6th [%]	7th [%]
1	24	> 99	> 99	94	98[a]	> 99	92	> 99[a]
2	12	> 99	> 99[a]	> 99[a]	> 99[a]	> 99[a]	99[a]	> 99[a,b]

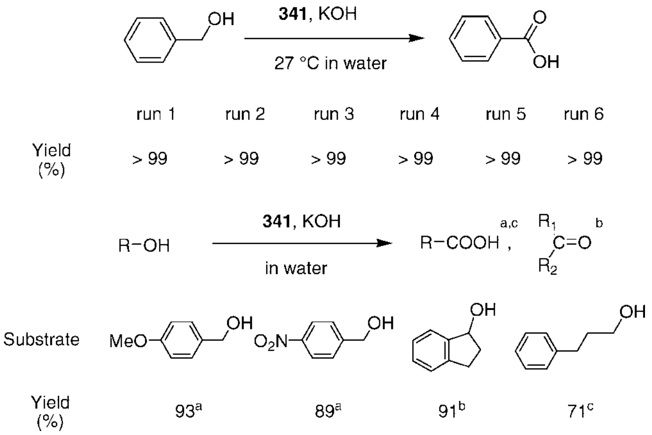
[a] The recovered catalyst was heated at 150 °C for 5 h without solvent in air bifore use.

[b] 8th: > 99%. 9th: 99%. 10th: > 99%.

Scheme 219



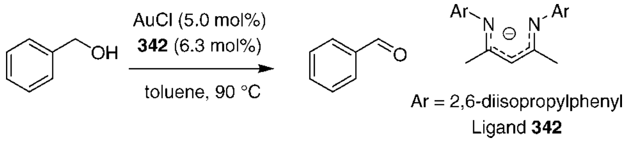
Scheme 220



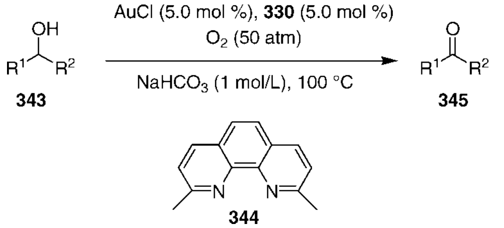
[a,b] [Substrate] 0 = 16.7 mM, [Au] = 0.33 mM, [KOH] = 50 mM, at 27 °C in water.

[c] [Au] = 0.66 mM, at 32 °C in water.

Scheme 221



Scheme 222



Scheme 223

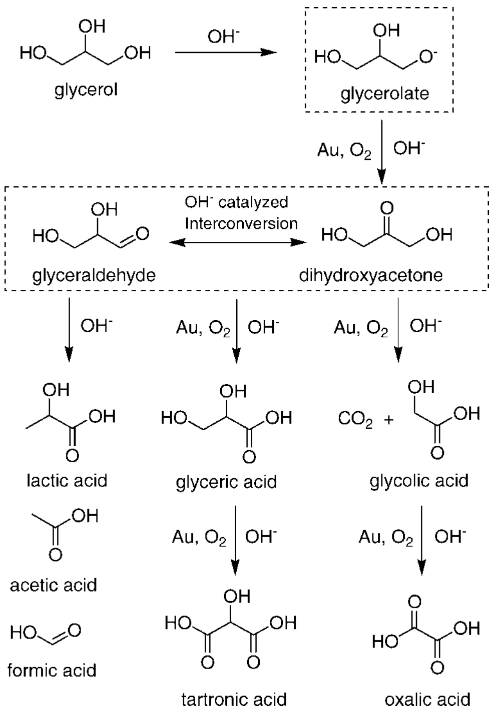
$$\mathrm{HOCH_2CH_2OH + MeOH + O_2 \longrightarrow HOCH_2COOMe + 2H_2O}$$

MGC (Methyl glycolate)

A selective liquid-phase aerobic oxidation process for the one-step direct production of methyl glycolate (MGC)[380] from ethylene glycol (EG) and methanol (MeOH) as starting materials has succeeded at Nippon Shokubai Co. Ltd. in a pilot-scale demonstration in 2004 with a capacity of tonnes per month. The key step of this process is a one-step liquid-phase air oxidation of alcohols over heterogeneous gold catalysts. The process is simple and the product MGC is obtained with a high purity over 98% (Scheme 223). The substrate-selectivity was observed clearly with Au catalyst, not with a typical Pd or Ru catalyst, which is also capable of catalyzing the oxidative esterification of alcohol. The substrate-selectivity observed with Au catalyst is the result of a competitive adsorption properties between MeOH (monodentate) and EG (bidentate) on the surface of Au particles. It suggests that the difference in adsorption properties between two substrates on catalyst surface would be much larger on the nanogold catalyst than on the other metal catalysts, which is the origin of the highly substrate-selectivity.

Gold-catalyzed oxidation of 1,2-diols, such as 1,2-ethanediol and 1,2-propanediol, resulted in a high chemoselectivity to α-hydroxy-carboxylates and high conversions in a wide pH range. Prati and Rossi showed that gold is a suitable alternative for platinum group catalysts because the surface of Au is not readily overoxidized and is hardly sensitive to chemical poisoning by acid adsorption.[381] The feasibility of using well-stabilized gold sols as pseudohomogeneous catalysts has been demonstrated.[382] Au sols emerged as active and chemoselective catalysts for the oxidation of aliphatic 1,2-diols. Because the reaction can be conducted in alcohol media, with only a small volume of water, even long chain aliphatic 1,2-diols can be smoothly converted. The need for an inorganic base such as NaOH in the reaction was examined. The alkali base is clearly indispensable. The base may fulfill at least two roles. First, the base may promote the dehydrogenation of the alcohol to the aldehyde by H^+ abstraction from the alcohol. Second, NaOH helps in desorbing the acid product from the metal surface by carboxylate formation. Temperature has likewise a well-defined effect on the catalytic activity. The decreasing catalytic activity at higher temperatures is likely caused by sol instability. After a 6 h oxidation run was performed at temperatures exceeding 353 K, aggregation of the sol catalyst with formation of a dark-colored deposit was observed. Two

Scheme 224



approaches were compared to recycle the pseudohomogeneous catalyst. First, poly(dimethylsiloxane) membrane filtration gives excellent preservation of activity, but a membrane reactor setup is required. Alternatively, at high solute concentrations, biphasic catalyst separation is possible, but the activity is less well preserved than with the membrane filtration. In optimized conditions, up to 2000 catalytic cycles can be performed per Au atom in the production of long chain α-hydroxy-alkanoates.

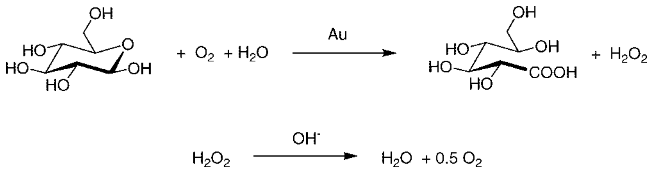
Conversion of glycerol is of interest because it is a byproduct of biodiesel production from plant and animal oils. A major surplus of glycerol has resulted from rapid expansion of biodiesel production capacity around the world. The oxidation of glycerol over Au catalysts is one possible route for using this biorenewable feedstock.[383] Gold catalysts operating in the aqueous phase have been shown to be highly active for the oxidation of glycerol.[384] Carbon-supported Au particles with mean sizes ranging from 5 to 42 nm and unsupported Au powder were evaluated as catalysts in the aqueous phase oxidation of glycerol.[385] Influence of gold particle size revealed that in the aqueous phase at 333 K larger particles and bulk Au are less active than 5 nm Au particles. However, large Au particles (>20 nm) were more selective to glyceric acid (Scheme 224). Moreover, the influence of the temperature was studied, and it was found that by increasing the temperature, only with a large particle size the formed glycerate was retained and not overoxidized to tartronate.[386]

The lower selectivity of small Au particles is attributed to a higher formation rate of H_2O_2 during glycerol oxidation, because peroxide promotes C−C cleavage reaction.[387]

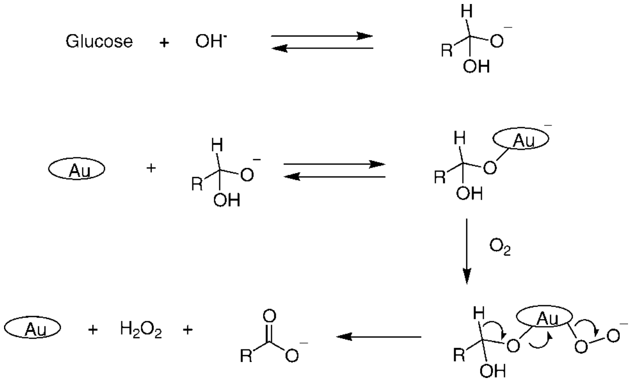
A number of Au/TiO_2 catalysts were synthesized using different preparation methods including various reduction procedures, and evaluated in the liquid phase oxidation of glycerol. It has been demonstrated that the use of different reduction method (calcination versus chemical reduction) has a crucial effect on the oxidation state of Au and on the gold particle dimension with consequence on the catalytic behavior in the liquid phase oxidation of glycerol.[388] Ceria-supported catalysts were compared with the performance of carbon- and titania-supported gold catalysts.[389] Focusing on the selective glycerol oxidation, carbon supported gold catalysts are, at the moment, still the best system to elaborate the selective glycerol oxidation. In fact, the reaction parameters and the preparation conditions of these carbon supported catalysts have an influence not only on the activity but also on the selectivity. Bimetallic catalysts can have markedly different activity and selectivity compared with the monometallic analogues.[390] Bimetallic catalysts of Au and Pd exhibited very high alcohol oxidation rates and selectivities.[391] Different synthesis methods were used for the preparation of Au−Pd bimetallic catalysts. The direct deposition of Au onto a parent Pd monometallic catalyst was successful for preparation of a series of Au on Pd catalysts. Catalyst characterization using TEM, H_2 titration, and XAS indicated that there may be a maximum Au coverage on the Pd after which additional Au deposited as monometallic clusters on the catalyst support. Nevertheless, the parent Pd catalyst maintained the Au in a highly dispersed state. In situ XAS characterization of the Pd catalyst and a Au−Pd bimetallic catalyst revealed good particle stability during aqueous-phase oxidation. Moreover, the Pd and Au appear to be metallic under reaction conditions. The preparation of Au−Pd sol gave a catalyst in which the Au almost completely covered the Pd.[392] It there is not a significant rate enhancement for the bimetallic catalysts compared with monometallic Au after rates have been properly normalized to the surface metal concentration. But there does appear to be an important influence of Pd on the selectivity of the glycerol oxidation reaction. Kinetic studies revealed that Pd in either a bimetallic particle or a physical mixture with Au decreased the amount of observed H_2O_2 in the reaction. Because H_2O_2 is correlated with the formation of C−C cleavage products, the presence of Pd with Au increased the selectivity of the glycerol oxidation reaction to the formation of glyceric acid. The liquid phase oxidation of glycerol with oxygen has also been studied using mono- and bimetallic catalysts based on Au and Pd metals supported on activated carbon or graphite[393] to study the effect of the metal on the distribution of the products and on activity of catalysts. It was found that by using bimetallic catalysts (Au−Pd) a strong synergistic effect was shown. By using a preformed nucleating center, Prati and co-workers[394] were able to obtain a single alloyed phase, which allowed the synergistic effect to be addressed to the presence of alloyed Au/Pd. The advantage of using this latter catalyst lies not only in the high activity but also in a prolonged catalyst life. Although a partial leaching of palladium and assembling of the particles have been revealed by ICP and HRTEM respectively, activity after 10 recycles decreased less than expected (about 10%).

Carbohydrates represent one of the most important sources of renewable materials. Special attention was paid to the selective catalytic oxidation of sugars because the aldonic acids obtained as main products can find many applications in the food and detergent industries, as well in cosmetics and medicine. Carbohydrate oxidation can be accomplished by chemical, biochemical and catalytic routes. The chemical and biochemical processes often display disadvantages as difficulties arise in the separation of the products, control of byproduct or disposal of wastewater. In this regard, heterogeneous catalysis in aqueous solutions seems to be a valuable, environmentally friendly alternative to the chemical

Scheme 225



Scheme 226

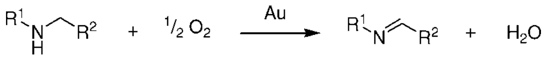


and enzymatic procedures for sugar oxidation. Various works dealt with the study of glucose oxidation on Pt(I) and Pd(II) catalysts. In general, platinum catalysts displayed only a mediocre selectivity, an additional doping with bismuth or lead being necessary to obtain better catalytic properties.[395] In the oxidation process of glucose, leaching of bismuth was evidenced.[396] Rossi and co-workers[397] reported for the first time glucose oxidation on a gold catalyst. Glucose was oxidized on immobilized gold colloids on carbon, and surprisingly, a total selectivity to gluconate was found. In particular, it has been shown that glucose can be efficiently oxidized to gluconate using supported and unsupported gold nanoparticles, gold catalysis being competitive with respect to enzymatic catalysis.[398] The kinetics of aerobic oxidation of glucose catalyzed by colloidal gold has been investigated[399] and compared with the enzymatic catalysis.[400] Careful analytic determinations showed that the gold-catalyzed aerobic oxidation of glucose occurs through a two-electron mechanism leading to gluconate and hydrogen peroxide (Scheme 225).[401]

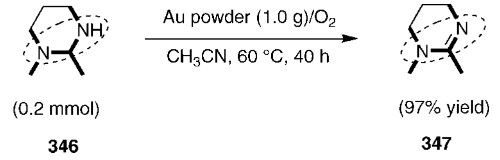
In the presence of alkali, hydrogen peroxide is mainly decomposed, before reaching a sufficient concentration for oxidizing glucose. Concerning the mechanism (scheme 226), the key point is represented by the electron-rich gold species, formed by the hydratated glucose anion with gold surface atoms, which is supposed to activate molecular oxygen by nucleophilic attack.

Peroxidic-like species already suggested as reaction intermediate during dihydrogen oxidation in water on a gold catalyst,[402] can be formally considered as a bridge for the two-electron transfer from glucose to dioxygen. To make a catalytic process more competitive, it is essential to use highly selective, stable, and active catalysts. More recent investigations of metal oxide-supported gold catalysts showed that such catalysts have excellent properties in the liquid-phase carbohydrate oxidation. Alumina-supported gold catalysts can be regarded as major breakthrough on the way to an industrial process of carbohydrate oxidation.[403] The prepared alumina-supported catalysts are very active in glucose oxidation and have, without exception, 100% selectivity toward D-gluconate. A continuous-flow liquid-phase oxidation using a gold catalyst has been described.[404] A 0.25% Au/Al_2O_3 catalyst was investigated in the continuous-flow carbohydrate oxidation using glucose as the model compound. The long-term stability of the gold catalyst was excellent as no loss in activity or selectivity occurred during 70 days of continuous operation. The preparation of gold catalysts for liquid-phase glucose oxidation by the incipient wetness method is a good alternative to preparation with deposition–precipitation. TEM analysis revealed that it is possible to prepare small gold particles with particle size of 2 nm by incipient wetness, even at high gold loadings. In glucose oxidation, the catalysts are very similar in terms of activity, selectivity, and long-term stability to those prepared by deposition–precipitation with urea as the precipitation agent. From ecological and economical standpoints, the incipient wetness method has some advantages.[405] The influence of doping an alumina support with different base metal oxides on the catalytic performance of gold catalysts to oxidize glucose to gluconic acid has been investigated.[406] Sodium oxide and calcium oxide strongly enhanced the reaction rate for catalysts prepared by both the deposition–precipitation and incipient wetness method. Urea was used as the precipitation agent in the former. The total selectivity of the catalysts was not influenced by the dopants. TEM analysis revealed very small gold particles of less than 2 nm for sodium-doped catalysts prepared by the two methods. Titania-supported catalysts, also, revealed remarkable properties regarding their catalytic activity in the oxidation of glucose.[407] The oxidation of various pentoses, hexoses, and di/oligosaccharides has been investigated on Au, Pd, and Pt catalysts.[408] In these reactions, the gold catalysts showed a very high activity and a total selectivity to the corresponding aldonic acids. In particular, the selective oxidation of disaccharides represents a challenging process because of the existence of at least three carbons exposed to oxidation in those molecules. It is quite problematic to design a catalyst that is able to distinguish between the anomeric hydroxyl on the one hand and the other two primary alcoholic groups on the other hand. Similar to the oxidation of pentoses and hexoses, the gold catalyst displayed the highest catalytic activity for the oxidation of disaccharides. Furthermore, two different gold catalysts (Au/TiO_2 and Au/Al_2O_3) were compared for the oxidation of maltose and lactose, respectively. Maltose and lactose are raw materials available in large amounts, and they constitute relevant renewable resources for industry. Their oxidation products, especially lactobionic acid, found many applications in different fields. Au/TiO_2 was used in maltose oxidation during 10 runs. A decrease in activity after the first run was found that was attributed to Au leaching, probably because of an insufficient stabilization of gold particles on the support. In spite of this, the catalyst displayed a good activity during the ten runs. The Au/Al_2O_3 catalyst was successfully used during 10 runs for the oxidation of lactose, and no important decrease of activity was noted. A permanently high selectivity of Au catalysts was always found for both oxidation reactions. Because of the noteworthy properties of gold catalysts, that is, total selectivity, high activity, excellent long-term stability, a new, versatile, and environmentally friendly preparation method of various aldonic acids was developed. Most of the obtained aldonic acids are not commercially available now, but the new method will allow their production in an economical way and, at the same time, provide an opportunity to enlarge the spectrum of their applications.

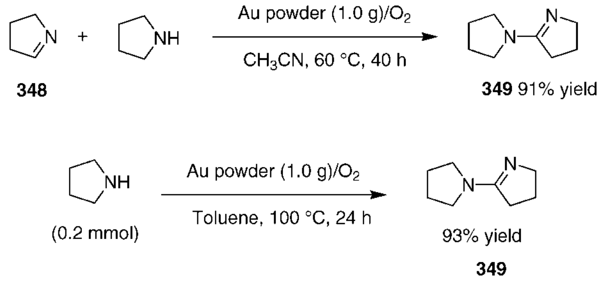
Scheme 227



Scheme 228



Scheme 229



6.3. Selective Oxidations of Amines

It is known that all types of amines are easily oxidized using appropriate reagents. The course of the reaction is quite variable and depends very much on the structure of the amine but, in general, hydrogen peroxide converts the primary amines into nitro compounds, whereas the secondary amines are oxidized to hydroxylamines. Tertiary amines are converted by hydrogen peroxide into the relative hydrated *N*-oxides that are transformed to *N*-oxides by heating under vacuum. Peroxodisulfuric and trifluoroperacetic acids oxidize aromatic amines to nitroderivatives. Very recently, it has been reported that bulk gold powder, which consists of particles (~1000 nm) much larger than nanoparticles, can catalyze, under mild conditions reactions, the aerobic oxidation of secondary amines to imines (Scheme 227).[409]

When the Au-catalyzed oxidation of **346** was carried out under the standard conditions, the expected imine **347** was produced in almost quantitative yield (Scheme 228).

For the less-hindered cyclic amines, a further step could occur under the reaction conditions. The imine derivative can undergo a subsequent addition reaction with the starting amine (Scheme 229). That this step could occur under the conditions of the reactions has been established by the reaction of Δ1-pyrroline with pyrrolidine **348**, which gives **349** directly in 91% yield. This reaction appears to be faster than the oxidative formation of the Δ1-pyrroline. The hydroamination reaction is also catalyzed by the Au as no reaction occurs in the absence of the Au. Especially surprising is the observation that no reaction occurs in the absence of O_2, which suggests that O_2 is required to activate the gold catalyst for the addition reaction of the pirrolidine to the Δ1-pyrroline.

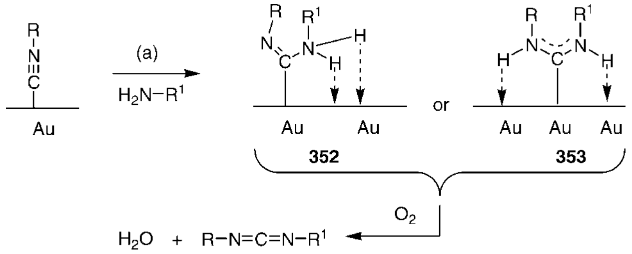
Interestingly enough, it appears that non-nanogold is capable of catalyzing several types of reactions. None of these reactions requires nanosized gold particles or supported gold even if the application of these results to the practical conversion of amines to imines requires making more efficient use of the gold.

A new application of gold catalysis in organic synthesis has been found by discovering the ability of supported mono- and bimetallic gold catalysts to transform tertiary amines into the corresponding *N*-oxides under "green" conditions, that is, working in aqueous solution with molecular oxygen under mild conditions.[410] Among different supporting materials, metals, and their binary combinations, the highest catalytic activity by reacting triethylamine with oxygen at 363 K to give trietylamine *N*-oxide was observed with the bimetallic Au−Rh on carbon system (100% conversion), where a synergistic effect is clear considering the lower conversion of Au/C (46%) and Rh/C (26%) catalysts. Moreover, Au/TiO_2 and the bimetallic Au−Pt on carbon also show high conversions. Alkali produced a strong negative effect. Pyridine has been also smoothly oxidized by oxygen in the presence of all the tested catalysts producing pyridine-*N*-oxide with 100% yield in two hours tests. No negative effects have been observed adding alkali to the reactants, and 100% yields were always obtained. The chemoselectivity of the oxidation of aminoalcohols of formula R_1R_2N-$(CH_2)_n$-CH_2OH depended upon the nitrogen substituents, catalyst composition, and experimental conditions. The reaction of 3-dimethylamino-1-propanol with O_2 in the presence of gold containing catalysts has been investigated as a model system. The oxidation of the amino group is favored in the absence and in the presence of alkali. In the absence of alkali, 100% selectivity has been observed in all the cases, but a high activity is restricted to gold-containing catalysts. Pt/C was inactive as the catalyst, and Rh/C produced only 20% conversion to unidentified compounds. This result is in line with the observation that aliphatic amines strongly interact with the traditional noble metals, resulting in the catalyst deactivation.[411]

Scheme 230

$$\underset{\mathbf{350}}{R{-}N{=}C} + H_2N{-}R^1 + {}^1\!/_2\,O_2 \xrightarrow{Au} \underset{\mathbf{351}}{R{-}N{=}C{=}N{-}R^1} + H_2O$$

Scheme 231



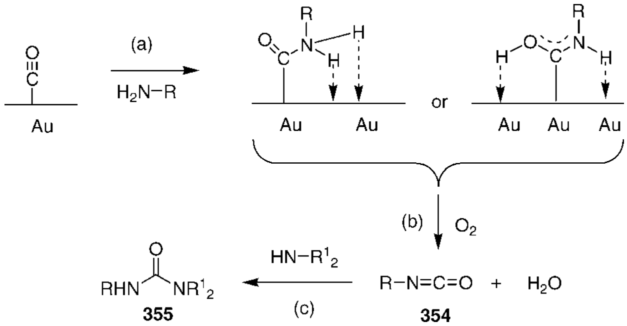
6.4. Oxidative Amination Reactions

Angelici reported[412] that bulk gold catalyze the oxidative amination of isocyanides **350** to give carbodiimides **351** according to the following Scheme 230

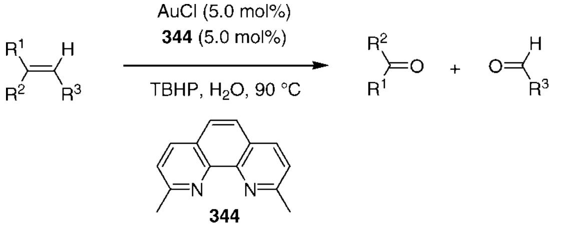
The catalyst was gold powder with a particle size of approximately 1 μm (10^3 nm). On the basis of studies of the adsorption of isocyanides on the Au powder,[413] identification of the carbodiimide product, and kinetic studies, a mechanism has been proposed (Scheme 231) in which the rate-determining step is amine attack on the adsorbed isocyanide carbon.

Intermediate **352** or **353** reacts by transferring hydrogen atoms to O_2 to give the presumed H_2O byproduct. Step (a) is analogous to the well-known attack of amines on isocyanide ligands in transition metal complexes.[414] Nevertheless, the Au-catalyzed reaction gives a carbodiimide product, whereas the homogeneous metal-ion-catalyzed reaction gives a formamidine.[415] For Au(I) and Au(III) complexes, the

Scheme 232



Scheme 233



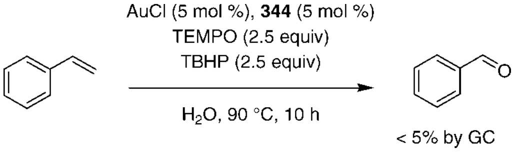
formamidine is liberated from the diaminocarbene complex only upon displacement by other ligands such as PPh_3 or CN^-.[416] It is apparently the ability of hydrogen atoms to transfer to the Au surface or to the O_2 that leads to the carbodiimide product, a pathway that is not available to the metal-ion-catalyzed reaction. The CO ligand, which is isoelectronic with isocyanides, is attacked by amines when ν(CO) is greater than approximately 2000 cm^{-1}. Although CO is not detectably adsorbed on bulk gold at room temperature, CO adsorbed at low temperatures on bulk Au or on Au nanoparticles gives ν(CO) values of approximately 2100 cm^{-1}, which suggests that CO adsorbed on Au should be susceptible to attack by amines. If the reaction of CO with primary amines were to follow the pathway for the reaction of isocyanides with primary amines and O_2, one would expect the product to be an isocyanate **354**, which in many cases would react with another primary amine molecule to give the final urea product **355** (Scheme 232). Indeed, it has been reported that the reaction of CO does occur, and it is catalyzed by bulk gold powder (~1000 nm particles) that does not have nanosized dimensions, under mild temperatures (45 °C) and at atmospheric pressures of the CO and O_2 gases.[417]

6.5. Oxidative Cleavage of Carbon−Carbon Double Bond

The cleavage of the C=C bond to form two carbonyl products is a synthetically useful method, which is usually achieved by ozonation followed by reduction or by dihydroxylation, followed by oxidation.[418] Metal-mediated olefin oxidation could represent a valuable alternative of great interest.[419] In this context, an interesting method to oxidize olefins to form ketones or aldehydes with the use of AuCl/neocuproine as the catalytic system and *tert*-butyl hydrogenperoxide (TBHP) as the oxidant has been developed (Scheme 233).[420] This oxidation reaction proceeds under mild conditions in water.

To exclude the gold(III) species as a potential catalyst under such an oxidizing condition, $AuCl_3$ was employed to replace AuCl. This reaction produced a mixture with only a small amount of carbonyl products, and most of the starting material was recovered. A range of substrates were investigated. Steric hindrance seems to be a key factor in affecting the rate of oxidation of these substrates. The bulky groups and the electron-withdrawing substitutions might affect the rate of oxidation because of their varied binding affinities to gold(I). It was also found that this oxidation was completely inhibited by TEMPO (Scheme 234), which may suggest a radical initiation pathway.

Scheme 234



Gold-catalyzed cleavage reactions of the C=C double bond to carbonyl compounds using molecular oxygen have also been explored.[421] Treatment of **356** with 2 mol % of AuCl(PPh3)/AgOTf in THF at 50 °C for 21 h in the atmosphere of O_2 (1 atm) afforded butenolide **357** in 90% yield (scheme 235). The byproduct of benzoic acid was isolated in 26% yield. No reaction was observed in the absence of Au(I). The results clearly indicated that Au(I) could catalyze the oxidative cleavage reaction efficiently. The gold(I) complex $AuClP(p\text{-}CF_3C_6H_4)_3$/AgOTf also showed good catalytic activity in THF to afford 92% of **357**. However, $AuCl_3$ was ineffective to this reaction. The use of solvent, such as 1,4-dioxane, CH_3CN, or 1,2-dichloroethane, resulted in a lower conversion or a prolonged reaction time. Normal olefins, such as 1-decene or styrene, are inert to oxidative cleavage under the same reaction conditions, whereas an enol ethers do react.

When oxygen was gently bubbled through a THF solution of (*Z*)-enynol **358** containing 2 mol % of cationic gold(I) complex $AuCl(PPh_3)$/AgOTf for 17 h at 50 °C, the butenolide **357** was formed in 97% yield. It was expected that benzaldehyde should be isolated as a byproduct; however, the amount of the initial formed benzaldehyde (detected by GC) gradually decreased during the reaction, and instead, benzoic acid was obtained in 64% yield (Scheme 236). A partial oxidation of THF was also observed. The presented results clearly demonstrate that Au(I) acted as a single-pot catalyst to catalyze cyclization to dihydrofurans **356**, followed by an oxidative cleavage reaction converting it to butenolides **357** directly. The cyclization occurred much faster than subsequent cleavage reaction. It is also indicated that the cyclization was not interfered with under the atmosphere of dioxygen.

6.6. Oxidative Cyclization Reaction of Enynes

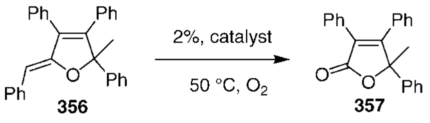
A new oxidative cyclization of 2-ethenyl-1-(prop-2′-yn-1′-ol)benzenes **359** to give naphthyl aldehydes and ketones using Pt and Au catalytic systems has been investigated (Scheme 237).[422]

The resulting metal−naphthylidene intermediates **363** in such cyclizations were identified and oxygenated by water and H_2O_2, respectively. The Au catalyst is far superior to platinum system for the production of the desired ketones and aldehydes from diverse alcohol substrates (Scheme 238).

7. Conclusion

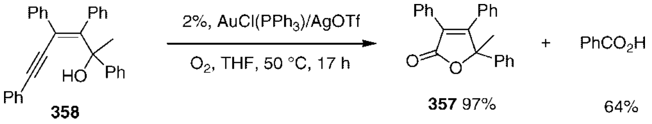
Both in heterogeneous and homogeneous catalysis, gold catalysts can carry out processes for which no other catalyst

Scheme 235

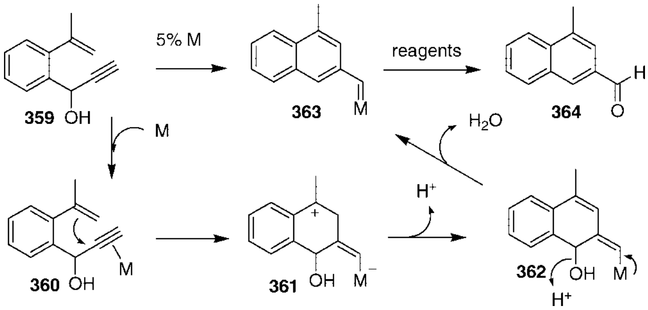


catalyst	yield
$(PPh_3)AuOTf$, THF, 21 h	90%
$P(o\text{-}CF_3C_6H_4)_3AuOTf$, THF, 14 h	92%
$(PPh_3)AuOTf$, 1,4-dioxane, 20 h	70%
$(PPh_3)AuOTf$, CH_3CN, 4 days	84%
$(PPh_3)AuOTf$, $(ClCH_2)_2$, 5 days	61%
$(PPh_3)AuOTf$, air, THF, 36 h	99%
$AuCl_3$, $(ClCH_2)_2$, 24h	6%

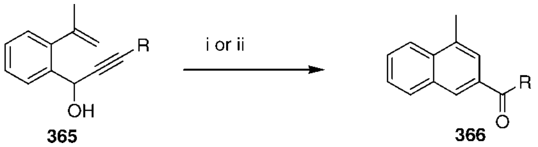
Scheme 236



Scheme 237



Scheme 238[a]



[a] R = ^{n}Pr; i = 25 °C, $PtCl_2$ (5%), CO (1 atm), 20 equiv H_2O, [substrate] = 0.27 M THF; **366** = 6% yield; ii= 70 °C, $AuClPEt_3$ (5%), H_2O_2 (3 equiv), [substrate] = 0.27 M DCE; **266** = 83% yield.

has yet been identified. Moreover gold is an intriguing alternative to platinum and palladium, with often superior characteristics. Soluble gold complexes have significant impact in the development of more efficient alternative synthetic methods. By virtue of their unique ability to activate carbon−carbon double and triple bonds as soft, carbophilic Lewis acids, gold complexes have been utilized as highly efficient catalysts for the formation of C−C, C−O, C−N, and C−S bonds, often in cyclization reactions. On the other hand, gold salts can operate as bifunctional Lewis acids activating either or both C−C multiple bonds or (and) make σ-complexes with heteroatoms providing highly selective transformations. The ability of gold salts to catalyze direct C−H bonds functionalization opens exciting developments. The application of gold catalysis in stereoselective synthesis can be accomplished through the preparation of chiral gold ligands tightly bound to the metal to induce asymmetric product distributions. Furthermore it was shown that the chiral counterion can be combined additively with chiral ligands to enable an asymmetric transformation that cannot be achieved by either method alone. Stereoselectivity will probably be the major challenge in this field in the future. The propensity of propargyl esters to undergo 1,2- and 1,3-acyl migration led to the formation of Au−carbene and Au−allene derivatives, respectively, which after subsequent functionalization, can allow for great molecular diversity.

A key technology that is bringing a breakthrough is catalysis by gold nanoparticles and clusters. When gold is prepared as very small particles with diameters of less than 10 nm and is highly dispersed on activated carbon or metal oxides or organic polymers, it turns to be a highly active catalyst for oxidation and hydrogenation reactions. Supported gold nanoparticles are selective and recyclable catalysts. The range of commercially interesting chemical reactions where gold performs well is substantial and increasing. Gold catalysis is therefore ready for industrial applications. From the literature presented, it is clear that gold offers many opportunities in developing new “green” technologies.

8. Acknowledgments

I thank the Ministero dell’Università e della Ricerca, Rome, and the University of L’Aquila for their support in the field of gold catalysis.

9. References

(1) (a) Horváth, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169.
(2) (a) Trost, B. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Trost, B. *Science* **1991**, *254*, 1471. (c) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505.
(3) (a) Kümmerer, K. *Green Chem.* **2007**, *9*, 899. (b) Höfer, R.; Bigorra, J. *Green Chem.* **2007**, *9*, 203.
(4) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007.
(5) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. *Appl. Catal. A: Gen.* **2001**, *221*, 3.
(6) Liu, S.; Xiao, J. *J. Mol. Catal. A: Chem.* **2007**, *270*, 1.
(7) For a general treatise, see: Bond, G. C.; Louis, C.; Thompson, D. T. *Catalysis by Gold*; Imperial College Press: London, 2006.
(8) Corti, C. W.; Holliday, R. C.; Thompson, D. T. *Top. Catal.* **2007**, *44*, 331.
(9) Hutchings, G. J. *Catal. Today* **2007**, *122*, 196.
(10) CatGoldNews, *Gold Bull.* **2007**, *40/2*, C1.]?>
(11) Gabbiani, C.; Casini, A.; Messori, L. *Gold Bull.* **2007**, *40*, 73.
(12) Nolan, P. S. *Nature* **2007**, *445*, 496.
(13) Sherry, B. D.; Toste, F. D. *Chemtracts Org. Chem.* **2005**, *18*, 14.
(14) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (e) Krause, N.; Morita, N. In *Comprehensive Organometellic Chemistry III*; Crabtree, R. C., Mingos, M., Eds.; Elsevier B. V.: Amsterdam, 2007; Vol. 9, p 501. (f) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211. (g) Hashmi, A. S. K.; Hutchings, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (h) Widenhoefer, R.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (i) Zhang, L.; S. J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (j) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916. (k) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (l) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (m) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (n) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (o) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (p) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (q) Dyker, G. In *Organic Synthesis*; Highlights, V., Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 48. (r) Dyker, G. *Angew Chem. Int. Ed.* **2000**, *39*, 4237. (s) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I.,Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 493. (t) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.

(15) (a) Pyykkö, P. *Inorg. Chim. Acta* **2005**, *358*, 4113. (b) Pyykkö, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4412. (c) Pyykkö, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3573.

(16) Ishida, T.; Haruta, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7154.

(17) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M; Hartwig, J. F. *Org. Lett.* **2006**, 8.

(18) (a) Larock, R. C. In *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: Berlin, 1986. (b) Freeman, F. *Chem. Rev.* **1975**, *75*, 439.

(19) (a) Olah, G. A.; Clifford, P. R. *J. Am. Chem. Soc.* **1971**, *93*, 2320. (b) Sakaki, S.; Maruta, K.; Ohkubo, K. *J. Chem. Soc., Dalton Trans.* **1987**, 361.

(20) (a) Yamamoto, H.; Sasaki, I.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 1399. (b) Biswas, G.; Ghorai, S.; Bhattacharjya, A. *Org. Lett.* **2006**, *8*, 313.

(21) (a) Hutchings, G. J.; Grady, D. T. *Appl. Catal.* **1985**, *16*, 411. (b) Hutchings, G. J.; Grady, D. T. *Appl. Catal.* **1985**, *17*, 155.

(22) Hutchings, G. J. *J. Catal.* **1985**, *96*, 292.

(23) (a) Nkosi, B.; Coville, N. J.; Hutchings, G. J.; Adams, M. D.; Friedl, J.; Wagner, F. E. *J. Catal.* **1991**, *128*, 378. (b) Nkosi, B.; Coville, N. J.; Hutchings, G. J.; Adams, M. D.; Friedl, J.; Wagner, F. E. *J. Catal.* **1991**, *128*, 366. (c) Nkosi, B.; Coville, N. J.; Hutchings, G. J. *Chem. Commun.* **1988**, 71. (d) Nkosi, B.; Coville, N. J.; Hutchings, G. J. *Appl. Catal.* **1988**, *43*, 33.

(24) Conte, M.; Carley, A. F.; Heirene, C.; Willock, D. J.; Johnston, P.; Herzing, A. A.; Kiely, C. J.; Hutchings, G. J. *J. Catal.* **2007**, *250*, 231.

(25) Mitchenko, S. A.; Khomutov, E. V.; Shubin, A. A.; Shul'ga, Y. M. *J. Mol. Catal. A* **2004**, *212*, 345.

(26) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *126*, 7736.

(27) (a) Hara, S. Stereoselective synthesis of monofluoroalkenes using cross coupling reactions. In*Fluorine Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005; pp 120−139. (b) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641.

(28) (a) Xu, J.; Burton, D. J. *J. Fluorine Chem.* **2007**, *128*, 71. (b) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720. (c) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405. (d) Nakamura, Y.; Okada, M.; Koura, M.; Tojo, M.; Saito, A.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2006**, *127*, 627.

(29) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121.

(30) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983.

(31) (a) Fukuda, Y.; Utimoto, K *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013. (b) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (c) Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

(32) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sans, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925.

(33) Schulz, M.; Teles, J. H. U.S. Patent 6,037,482 for BASF, Mar. 14, 2000.

(34) Teles, J. H.; Schulz, M. WO-A1 9721648, 1997.

(35) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.

(36) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489.

(37) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563.

(38) Mizushima, E.; Cui, D.; Nath, D. C. D.; Hayashi, T.; Tanaka, M. *Org. Synth.* **2006**, *83*, 55.

(39) Keinan, E.; Sinha, S. C; Sinha-Bagchi, A. *J. Org. Chem.* **1992**, *57*, 3631.

(40) Deetlefs, M.; Raubenheimer, H. G.; Esterhuysen, M. W. *Catal. Today* **2002**, *72*, 29.

(41) Roembke, P.; Schmidbaur, H.; Cronje, S.; Raubenheimer, H. J. *Mol. Catal.* **2004**, *212*, 35.

(42) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. Z. *Anorg. Allg. Chem.* **2003**, *629*, 2363.

(43) Raubenheimer, H. G.; Cronje, S. J. *Organomet. Chem.* **2001**, *617−618*, 170.

(44) Sanz, S.; Jones, L. A.; Mohr, F.; Laguna, M. *Organometallics* **2007**, *26*, 952.

(45) Wessig, P.; Teubner, J. *Synlett* **2006**, 1543.

(46) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc* **2006**, *128*, 9620.

(47) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 1439.

(48) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187. (b) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (c) Wiley, R.; Jarboe, C. H.; Hayes, F. N. *J. Am. Chem. Soc.* **1957**, *79*, 2602. (d) Heilbron, I. M.; Jones, E. R. H.; Smith, P.; Weedon, B.C. L. *J. Chem. Soc.* **1946**, 54.

(49) (a) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 10405. (b) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

(50) (a) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019. (b) Dalla, V.; Pale, P. *New J. Chem.* **1999**, *23*, 803. (c) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1986**, *28*, 6647.

(51) Mc Donald, F.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648.

(52) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949.

(53) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* **2000**, *41*, 9195.

(54) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed* **2007**, *46*, 279.

(55) McMahon, T.; Silke, J. *Harmful Algae News* **1996**, *14*, 2.

(56) (a) Gleiser, L. K.; Nguyen, S.; Forsyth, C. J. *Org. Lett.* **2004**, *6*, 4159. (b) Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 4318.

(57) Jung, H. H.; Floreancig, P. E. *Org. Lett.* **2006**, *8*, 1949.

(58) (a) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319. (b) Trost, B. M.; Yang, H.; Wuitschik, G. *Org. Lett.* **2005**, *7*, 4761.

(59) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.

(60) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976.

(61) Oh, C. H.; Jik, H.; Lee, J. H. *New. J. Chem.* **2007**, *31*, 835.

(62) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.- G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191.

(63) Tian, G.-Q.; Min Shi, M. *Org. Lett.* **2007**, *9*, 4917.

(64) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodaríguez, F.; Fañanás, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091.

(65) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

(66) (a) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949. (b) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.

(67) Yang, T.; Campbell, L.; Dixon, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12070.

(68) (a) Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *Arkivoc* **2007**, 67. (b) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112.

(69) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273.

(70) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.

(71) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517–20.

(72) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515.

(73) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717.

(74) (a) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3553. (b) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763. (c) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727. (d) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

(75) Lim, C.; Kang, J.-E.; Ji-Eun Lee, J.-E; Shin, S. *Org. Lett.* **2007**, *9*, 3539.

(76) Patil, T. N.; Yamamoto, Y. *Arkivoc* **2007**, 6.

(77) Abad, A.; Corma, A.; García, H. *Top. Catal.* **2007**, *44*, 237.

(78) Asao, N. *Synlett* **2006**, 1645.

(79) Hildebrandt, D.; Dyker, G. *J. Org. Chem.* **2006**, *71*, 6729.

(80) Asao, N.; Sato, K. *Org. Lett.* **2006**, *8*, 5361.

(81) Asao, N.; Aikawa, H. *J. Org. Chem.* **2006**, *71*, 5249.

(82) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878.

(83) Crome, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435.

(84) (a) Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160.

(85) (a) Dubé, P.; Toste, D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (b) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274.

(86) (a) Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817. (b) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Anne-Lise Dhimane, A.-N.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207.

(87) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653.

(88) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985.

(89) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.

(90) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442.

(91) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414.

(92) Wang, S. Z.; Zhang, L. M. *Org. Lett.* **2006**, *8*, 4585.

(93) (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (b) Jimenez-Nunez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, 5452.

(94) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147.

(95) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021.

(96) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(97) (a) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996. (b) Hachiya, I.; Shibuya, H.; Shimizu, M. *Tetrahedron Lett.* **2003**, *44*, 2061.

(98) (a) Fukuyama, T.; Higashibeppu, Y.; Yamaura, R.; Ryu, I. *Org. Lett.* **2007**, *9*, 587. (b) Kishimoto, Y.; Mitani, I. *Synlett* **2005**, 2141.

(99) (a) Hua, R.; Tanaka, M. *New J. Chem.* **2001**, *25*, 179. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

(100) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250.

(101) Piera, J.; Krumlinde, P.; Strűbing, D.; Bǎckvall, J.-H. *Org. Lett.* **2007**, *9*, 2235.

(102) (a) Piera, J.; Närhi, K.; Bǎckvall, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6914. (b) Närhi, K.; Franzén, J.; Bāckvall, J. E. *Chem.—Eur. J.* **2005**, *11*, 6937. (c) Franzén, J.; Bāckvall, J. E. *J. Am. Chem. Soc.* **2003**, *125*, 6056.

(103) Asao, N.; Aikawa, H.; Tago, S.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299.

(104) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Li-Na Guo, L.-N.; Chen-Ze Qi, C.-Z.; Lianga, Y.-M. *Adv. Synth. Catal.* **2007**, *349*, 2493.

(105) (a) Beller, M.; Tillack, A.; Seayad, J. In *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 403. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (c) Hong, S.; Marks, T. *J. Acc. Chem. Res.* **2004**, *37*, 673. (d) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001; pp. 91.

(106) Severin, R; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407.

(107) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

(108) (a) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975. (b) Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297.

(109) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610.

(110) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, B.; Marinelli, F. J. *Org. Chem.* **2005**, *70*, 2273.

(111) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958.

(112) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, 1775.

(113) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627.

(114) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.

(115) (a) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, *10*, 1579. (b) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org.Chem.* **2001**, *66*, 6339. (c) Tokunaga, M.; Ota, M.; Haga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2001**, *42*, 3865. (d) Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017.

(116) Larock, R. C.; Leong, W. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, p 290.

(117) Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett.* **2005**, *7*, 267.

(118) Corma, A.; Concepciòn, P.; Dominguez, I.; Fornés, V.; Sabater, M. J. *J. Catal.* **2007**, *251*, 39.

(119) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645.

(120) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537.

(121) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905.

(122) Ritter, S.; Horino, Y.; Lex, J.; Schmalz, H.-G. *Synlett* **2006**, 3309.

(123) (a) Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2383. (b) Ohe, K.; Matsuda, H.; Ishihara, T.; Chatani, N.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1991**, *56*, 2267. (c) Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887.

(124) Yeom, H.-S; Lee, E.-S.; Shin, S. *Synlett* **2007**, 2292.

(125) Foot, O. F.; Knight, D. W.; Low, A. C. L.; Li, Y. *Tetrahedron Lett.* **2007**, *48*, 647.

(126) For Hg(II)-promoted reaction of alkyl azides with alkenes, see: Pearson, W. H.; Hutta, D. A.; Fang, W. *J. Org. Chem.* **2000**, *65*, 8326.

(127) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.

(128) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289.

(129) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709.

(130) (a) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (b) Ouh, L. L.; Müller, T. E.; Yan, Y. K. *J. Organomet. Chem.* **2005**, *690*, 3774. (c) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (d) Muzart, J. *Tetrahedron* **2005**, *61*, 5955. (e) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949. (f) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018.

(131) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050.

(132) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433.

(133) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker: New York, 1984.

(134) Lee, K. C.; Moon, B. S.; Lee, J. H.; Chung, K.-H.; Katzenellenbogen, J.A.; Chi, D. Y. *Bioorg. Med. Chem.* **2003**, *11*, 3649.

(135) (a) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339. (b) Pradhan, T. K.; Ghosh, S. C.; De, A. *ARKIVOC* **2003**, *9*, 158. (c) Katritzky, A. R.; Denisenko, S. N.; Oniciu, D. C.; Ghiviriga, I. *J. Org. Chem.* **1998**, *63*, 3450.

(136) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339.

(137) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

(138) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081.

(139) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192.

(140) Erdsak, J.; Krause, N. *Synthesis* **2007**, 3741.

(141) Hoffmann-Rőder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.

(142) (a) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038. (b) Youn, S. W.; Kim, Y. H.; Hwang, J.-W.; Ho, Y. *Chem. Commun.* **2001**, 996. (c) Krause, N.; Laux, M.; Hoffmann-Röder, A. *Tetrahedron Lett.* **2000**, *41*, 9613. (d) Hormuth, S.; Reissig, H.-U. *Synlett* **1991**, 179.

(143) (a) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104. (b) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (c) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743.

(144) (a) Xu, D.; Li, Z.; Ma, S. *Chem.—Eur. J.* **2002**, *8*, 5012. (b) Aurrecoechea, J. M.; Solay, M. *Tetrahedron* **1998**, *54*, 3851. (c) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 4913.

(145) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790.

(146) Marshall, J. A.; Pinney, K.G. *J. Org. Chem.* **1993**, *58*, 7180.

(147) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2003**, 1759.

(148) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519.

(149) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

(150) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658.

(151) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038.

(152) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066.

(153) Zhang, Z.; Widenhoefer, A. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 283.

(154) (a) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. (b) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550. (c) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1991**, *32*, 6359. (d) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *Chem. Commun.* **1987**, 243. (e) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997.

(155) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

(156) (a) Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614. (b) Ackermann, L.; Bergmann, R. G. *Org. Lett.* **2002**, *4*, 1475.

(157) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 1195.

(158) (a) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Can. J. Chem.* **2005**, *83*, 569. (b) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Synthesis* **2004**, *12*, 2186.

(159) Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.

(160) Phil Ho Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Hyunseok Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840.

(161) Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 4794.

(162) (a) Morita, N.; Norbert Krause, N. *Eur. J. Org. Chem.* **2006**, 4634. (b) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121.

(163) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887.

(164) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452.

(165) Hashmi, A. S. K. *Nature* **2007**, *449*, 292.

(166) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

(167) (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923. (b) Sweeney, Z. K.; Salsman, J. L.; Andersen, R. A.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2339.

(168) (a) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853.

(169) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314.

(170) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767.

(171) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897.

(172) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966.

(173) (a) Larock, R. C.; Leong, W. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York,

1991; Vol. *4*, p 297. (b) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (c) Harding, K. E.; Tinger, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 463. (d) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissing, H. U., Eds.; VCH: Weinheim, Germany, 1991; p 157. (e) Larock, R. C. *Solvomercuration/ Demercuration Reactions in Organic Synthesis*; Springer-Verlag: Berlin, 1986; Chapter 3.

(174) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(175) Reich, N. W.; Yang, C.-G.; Shi, Z.; He, C. *Synlett* **2006**, 1278.

(176) Nguyen, R.-V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397.

(177) Zhang, X.; Corma, A. *Chem. Commun.* **2007**, 3080.

(178) Smith, M. B.; March, J. *March's Adanced Organic Chemistry*; John Wiley and Sons: New York, 2001; p 993.

(179) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

(180) (a) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (b) Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331. (c) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507. (d) Vo, L. K.; Singleton, D. A. *Org. Lett.* **2004**, *6*, 246. (e) Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshijufi, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4501.

(181) (a) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (b) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

(182) (a) Kaspar, L. T.; Benjamin, F.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972. (b) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519. (c) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515.

(183) (a) Wei, H.; Qian, G.; Xia, Y.; Li, K.; Li, Y.; Li, W. *Eur. J. Org. Chem.* **2007**, 4471. (b) Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601.

(184) (a) Taylor, J. G.; N.; Whittall, J. G.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561. (b) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635.

(185) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

(186) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *13*, 2707.

(187) Han, X.; Widenhofer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

(188) Bender, C. F.; Widenhofer, R. A. *Org. Lett.* **2006**, *8*, 5303.

(189) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704.

(190) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043.

(191) Shi, W.-J.; Liu, Y.; Butti, P.; Togni, A. *Adv. Synth. Catal.* **2007**, *349*, 1619.

(192) (a) Brower, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744. (b) After our submission, a study of the reaction mechanism of the hydroamination of alkenes catalyzed by gold(I)-phosphine appeared, see: Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.

(193) Griesbaum, K. *Angew. Chem., Int. Ed.* **1970**, *9*, 273.

(194) Belley, M.; Zamboni, R. *J. Org. Chem.* **1989**, *54*, 1230.

(195) Brouwer, C.; Rahaman, R.; He, C. *Synlett* **2007**, 1785.

(196) Yamamoto, Y. J. *Org. Chem.* **2007**, *72*, 7817.

(197) (a) Fu, G. C. *J. Org. Chem.* **2004**, *69*, 3245–3249. (b) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307. (c) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733. (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (e) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. *1*, 2.

(198) (a) Olah, G. A.; Khrisnamurti, R.; Surya Prakash, G. K. *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, p 293. (b) Roberts, R. M.; Khalaf A. A. *Friedel-Crafts Alkylation Chemistry. A Century of Discovery*; Marcel Dekker: New York, 1984.

(199) Computations were performed with Gaussian 03. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(200) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443.

(201) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Tetrahedron* **2003**, *59*, 4661.

(202) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715.

(203) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525.

(204) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959.

(205) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203.

(206) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811.

(207) Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F. *Green Chem.* **2003**, *5*, 64–67.

(208) Arcadi, A.; Alfonsi, M.; Bianchi, G.; D'Anniballe, G.; Marinelli, F. *Adv. Synth. Catal.* **2006**, *348*, 331.

(209) Arcadi, A.; Alfonsi, M.; Marinelli, F. *J. Organomet. Chem.* **2007**, *692*, 5322.

(210) Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett.* **2005**, *7*, 5857.

(211) (a) Hashmi, A. S. K.; Schwarz, L.; Rubenbauer, P.; Blanco, M. C. *Adv. Synth. Catal.* **2006**, *348*, 705. (b) Nair, V.; Abhilash, K. G *Synthesis* **2006**, 3647.

(212) Nair, V.; Vidya, N.; Abhilash, K. G. *Tetrahedron Lett.* **2006**, *47*, 2871.

(213) (a) Diker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247. (b) Hashmi, A. S. K; Schwarz, L; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.

(214) Aguilar, D.; Contel, M.; Navarro, R.; Urriolabeitia, E. P. *Organometallics* **2007**, *26*, 4604.

(215) (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049. (b) Hashmi, A. S. K.; Salathé, R.; Frost, T. M.; Schwarz, L.; Choi, J.-H. *Appl. Catal. A: General* **2005**, *291*, 238.

(216) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944.

(217) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Eur. J. Org. Chem.* **2007**, 1648.

(218) Alfonsi, M.; Arcadi, A.; Bianchi, B.; Marinelli, F.; Nardini, A. *Eur. J. Org. Chem.* **2006**, 2393.

(219) Yao, T.; Zhang, X.; Larock, R. C. *J.Am. Chem. Soc.* **2004**, *126*, 11164.

(220) Liu, X.; Pan, Z.; Shu, X.; Duan, X.; Liang, Y. *Synlett* **2006**, 1962.

(221) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531.

(222) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445.

(223) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704.

(224) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462.

(225) Luo, Y.; Li, C.-J. *J.Chem. Soc., Chem. Commun.* **2004**, 1930.

(226) Youm, S. W. *J. Org. Chem.* **2006**, *71*, 2521.

(227) (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465. (c) Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron* **2004**, *60*, 12075.

(228) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

(229) (a) Sawamura, M.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 2723. (b) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649.

(230) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215.

(231) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235.

(232) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 239.

(233) Komiya, S.; Sone, T.; Usui, Y.; Hirano, M.; Fukuoka, A. *Gold Bull.* **1996**, *29* (4), 131.

(234) Xu, L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482.

(235) Marciniec, B.; Gulinski, J.; Maciejewski, H. in: Horváth, I. T.; E. Iglesia, E.;. Klein, M. T.; Lercher, J. A.; Russell, J. A.; Stieffel, E. I., Eds. *Encyclopedia of Catalysis*; Wiley-Interscience: New York, 2003; Vol. 4, p. 107.

(236) Ito, H.; Yajima, T.; Tateiwa, J. I.; Hosomi, A. *Chem.Commun.* **2000**, 981.

(237) Wile, B. M.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Organometallics* **2007**, *26*, 1069.

(238) Lantos, D.; Contel, M.; Sanz, S.; Bodor, A.; Horváth, I. T *J. Organomet. Chem.* **2007**, *692*, 1799.

(239) Debono, N.; Iglesias, M.; Sánchez, F. *Adv. Synth. Catal.* **2007**, *349*, 2470.

(240) Lantos, D.; Contel, M.; Larrea, A.; Szabó, D.; Horváth, I. T. *QSAR Comb. Sci.* **2006**, *25*, 719.

(241) Corma, A.; González-Arellano, Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7820.

(242) Cho, W. K.; Lee, J. K.; Kang, S. M.; Shik, Y.; Lee, H.-S.; Choi, I. S. *Chem.—Eur. J.* **2007**, *13*, 6351.

(243) Eds.: Shibasaki, M.; Yamamoto, Y. *Multimetallic Catalysts in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2004.

(244) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3296.

(245) (a) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835. (b) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605. (c) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (d) Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, D. *Org. Lett.* **2005**, *7*, 2501. (e) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (f) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

(246) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(247) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964.

(248) Terrason, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063.

(249) (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Dyker, G. In *Handbook of C−H Activation*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2005. (c) Periana, R.; Jones, C. J.; Taube, D.; Ziatdinov, V.; Nielsen, R.; Oxgaard, J.; Goddard, W. A., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 4626. (d) Shul'pin, G. B.; Shilov, A. E.; Süss-Fink, G. *Tetrahedron Lett.* **2001**, *42*, 7253. (e) Boring, E.; Geletii, Y. V.; Hill, C. L. *J. Am. Chem. Soc.* **2001**, *123*, 1625. (f) Nesmeyanov, A. N.; Grandberg, K. I.; Dyadchenko, V. P.; Lemenovskii, D. A.; Perevalova, E. G. *Izv. Akad. Nauk SSSR Ser. Khim.* **1974**, 1206 CAN 81:49772.

(250) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Synlett* **2007**, 1391.

(251) (a) Li, C.-J.; Yao, X. *Organic Synthesis* **2007**, *84*, 222. (b) Yao, X.; Li, C.-J *J. Am. Chem. Soc.* **2004**, *126*, 6884.

(252) Yao, X.; Li, C.-J *J. Org. Chem. Soc.* **2005**, *70*, 5752.

(253) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673.

(254) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828.

(255) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 1413.

(256) (a) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int Ed* **2004**, *43*, 5350.

(257) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486.

(258) Pan, J.-H; Yang, M.; Gao, Q.; Zhu, N.-Y.; Yang, D. *Synthesis* **2007**, 2539.

(259) Hashmi, A. S. K.; Scähfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184.

(260) Skouta, R.; Li, C.-J. *Angew. Chem.* **2007**, *46*, 1117.

(261) (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (b) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155.

(262) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542.

(263) (a) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (b) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964.

(264) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053.

(265) (a) Porter, K. A.; Schier, A.; Schmidbaur, H. *Organometallics* **2003**, *22*, 4922. (b) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330. (c) de Graaf, P. W. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1976**, *105*, 399. (d) Liddle, K. S.; Parkin, C. *J. Chem. Soc., Chem. Commun* **1972**, 26.

(266) (a) Partyka, D. V.; Esswein, A. J.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *26*, 3279. (b) Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 8188.

(267) Sun, X.; Wei Sun, W.; Fan, R.; Wua, J. *Adv. Synth. Catal.* **2007**, *349*, 2151.

(268) Schneider, M. R. ; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 8493.

(269) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Veerendhar, R. G.; Nagaiah, K. *Tetrahedron Lett.* **2001**, *42*, 8067.

(270) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

(271) Reets, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485.

(272) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358.

(273) Hashmi, A. S. K.; Wölfle, M.; Ata, F.; Hamzic, M.; Sálate, R.; Frey, W. *Adv. Synth. Catal.* **2006**, *348*, 2501.

(274) Hashmi, A. S.K.; Ata, F.; Bats, J. W.; Blanco, M. C.; Frey, W; Hamzic, M.; Rudolph, M; Salathé, R; Schäfer, S; Wölfle, M. *Gold Bull* **2007**, *40/1*, 31.

(275) Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2006**, *348*, 1283.

(276) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejovic, E.; Frost, T. M.; Miehlich, B.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2006**, *12*, 5806.

(277) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 6991.

(278) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Rivas Nass, A.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 5376.

(279) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754.

(280) (a) Hashmi, A. S. K; Wolfe, M.; Ata, F; Hamzic, M; Salathé, R.; Frey, W *Adv. Synth. Catal.* **2006**, *348*, 2501. (b) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wolfle, M.; Frey, W.; Bats, J. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2798. (c) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6545.

(281) Hashmi, A. S. K.; Ata, F.; Kurpejovic, E.; Huck, J.; Rudolph, M. *Top. Catal.* **2007**, *44*, 245.

(282) Hashmi, A. S. K.; Wölfle, M.; Teles, J. H.; Frey, W. *Synlett* **2007**, 1747.

(283) Hashmi, A. S. K.; Kurpejovic, E.; Wölfle, M.; Frey, W.; Bats, J. W *Adv. Synth. Catal* **2007**, *349*, 1743.

(284) Hashmi, A. S. K.; Kurpejoviæc, E; Frey, W; Bats, J. W. *Tetrahedron* **2007**, *63*, 5879.

(285) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709.

(286) Hashmi, A. S. K.; Blanco, C. *Eur. J. Org. Chem.* **2006**, 4340.

(287) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750.

(288) Marion, S.; Díez-González, S.; de Frémont, P.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647.

(289) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genet, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427.

(290) Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049.

(291) Amijs, C. H.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698.

(292) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821.

(293) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.

(294) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784.

(295) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876–5880.

(296) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058.

(297) Skouta, R.; Li, C.-J. *Synlett* **2007**, 1759.

(298) Sanz, S.; Laguna, M. *Catal. Today* **2007**, *122*, 403.

(299) (a) González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536. (b) Corma, A.; González-Arellano, C; Iglesias, M; Pérez-Ferreras, S; Sánchez, F *Synlett* **2007**, 1771.

(300) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.

(301) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

(302) (a) Yan, W.; Wang, R.; Xu, Z.; Xu, J.; Lin, L.; Shen, Z.; Zhou, Y. J. *Mol. Catal. A: Chem.* **2006**, *255*, 81. (b) Zhang, Y.; Santos, A. M.; Herdtweck, E.; Mink, J.; Kuhn, F. E. *New J. Chem.* **2005**, *29*, 366. (c) Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473.

(303) (a) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001. (b) Syeda, H. Z. S.; Halder, R.; Karla, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676. (d) Ju, Y.; Li, C. J.; Varma, R. S. *QSAR Comb. Sci.* **2004**, 23.

(304) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319.

(305) Hua, L. P.; Lei, W. *Chin. J. Chem.* **2005**, *23*, 1076.

(306) Li, C. J.; Wei, C. *Chem. Commun* **2002**, 268.

(307) Zhang, L.; Wei, C.; Varma, R. S.; Li, C. J. *Tetrahedron Lett.* **2004**, *45*, 2443.

(308) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Sridhar, B. *Tetrahedron Lett.* **2004**, *45*, 7319.

(309) Kantam, M. L.; Balasubrahmanyan, V.; Kumar, K. B. S.; Venkanna, G. T. *Tetrahedron Lett.* **2007**, *48*, 7332.

(310) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Mol. Div.* **2003**, *7*, 135.

(311) Sreedhar, B.; Reddy, P. S.; Prakash, B. V.; Ravindra, A. *Tetrahedron Lett.* **2005**, *46*, 7019.

(312) Kidwai, M.; Bansal, V.; Kumarb, A.; Mozumdar, S. *Green Chem.* **2007**, *9*, 742.

(313) Huang, B.; Yao, X.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1528.

(314) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529.

(315) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323.

(316) Claus, P. *Appl. Catal. A: General* **2005**, *291*, 222.

(317) Corma, A.; Gutiérrez-Puebla, E.; Iglesias, M.; Monge, A.; Pérez-Ferreras, S.; Sánchez, F. *Adv. Synth. Catal.* **2006**, *348*, 1899.

(318) Comas-Vives, A.; González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F.; Ujaque, G. *J. Am. Chem. Soc.* **2006**, *128*, 4756.

(319) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *Chem. Commun.* **2005**, 3451.

(320) (a) *Ullmann's Encyclopedia of Technical Chemistry, Electronic Release*, 6th ed.; Wiley-VCH: Weinheim, Germany, 2000. (b) Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem.* **2000**, *112*, 3106. (c) Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavour Materials*; Wiley-VCH: Weinheim, Germany, 1997.

(321) (a) Campo, B.; Volpe, M.; Ivanova, S.; Touroude, R. *J. Catal.* **2006**, *242*, 162. (b) Zanella, R.; Louis, C.; Giorgio, S.; Touroude, R. *J. Catal.* **2004**, *223*, 328. (c) Mohr, C.; Hofmeister, H.; Radnik, J.; Claus, P. *J. Am. Chem. Soc.* **2003**, *125*, 1905. (d) Mohr, C.; Hofmeister, H.; Claus, P. *J. Catal.* **2003**, *213*, 86. (e) Claus, P.; Brückner, A.; Mohr, C.; Hofmeister, H. *J. Am. Chem. Soc.* **2000**, *122*, 11430. (f) Milone, C.; Tropeano, M. L.; Gulino, G.; Neri, G.; Ingoglia, R.; Galvagno, S. *Chem. Commun.* **2002**, 868. (g) Baillie, J. E.; Abdullah, H. A.; Anderson, J. A.; Rochester, C. H.; Richardson, N. V.; Hodge, N.; Zhang, J.-G.; Burrows, A.; Kiely, C. J.; Hutchings, G. J. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4113. (i) Bailie, J. J.; Hutchings, G. J. *Chem. Commun.* **1999**, 2151.

(322) (a) Milone, C.; Ingoglia, R.; Schipilliti, L.; Crisafulli, C.; Neri, G.; Galvagno, S. *J. Catal.* **2005**, *236*, 80. (b) Milone, C.; Ingoglia, R.; Pistone, A.; Neri, G.; Frusteri, F.; Galvagno, S. *J. Catal.* **2004**, *222*, 348. (c) Milone, C.; Ingoglia, R.; Tropeano, M. L.; Neri, G.; Frusteri, F.; Galvagno, S. *Chem. Commun.* **2003**, 868.

(323) Milone, C.; Crisafulli, C.; Invoglia, R.; Schipilliti, L.; Galgano, S. *Catal. Today* **2007**, *122*, 341.

(324) Mertens, P. G. N.; Poelman, H.; Ye, X.; Vankelecom, I. F. J.; Jacobs, P. A.; De Vos, D. E. *Catal. Today* **2007**, *122*, 352.

(325) (a) Comas-Vives, A.; Gonzalez-Arellano, C.; Corma, A.; Iglesias, M.; Sanchez, F.; Ujaque, G. *J. Am. Chem. Soc.* **2006**, *128*, 4756. (b) Zhang, X.; Shi, H.; Xu, B. Q. *Angew. Chem.* **2005**, *117*, 7294. (c) Guzman, J.; Gates, B. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 690.

(326) (a) Thomas, J. M.; Raja, R.; Lewis, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 6456. (b) Böhme, D. K.; Schwarz, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2336.

(327) Liu, Z.-P.; Wang, C.-M.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6865.

(328) Zhang, X.; Shi, H.; Xu, B.-Q. *Catal. Today* **2007**, *122*, 330.

(329) Corma, A.; Serna, P. *Science* **2006**, *313*, 332.

(330) (a) Varma, R. S.; Kabalka, W. *Chem. Lett.* **1985**, 243. (b) Lee, S. H.; Park, Y. J.; Yoon, C. M. *Org. Biomol. Chem.* **2003**, *1* (7), 1099.

(331) Corma, A.; Serna, P.; Garcia, H. *J. Am. Chem. Soc.* **2007**, *129*, 6358.

(332) Corma, A.; Concepción, P.; Serna, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7266.

(333) (a) Thompson, D. T. *Top. Catal.* **2006**, *38*, 231. (b) Haruta, M. *Nature* **2005**, *437*, 1098.

(334) Nijhuis, T. A.; Makkee, M.; Moulijn, J. A.; Weckhuysen, B. M. *Ind. Eng. Chem. Res.* **2006**, *45*, 3447.

(335) (a) Corti, C. W.; Holliday, R. J.; Thompson, D. T. *Appl. Catal., A* **2005**, *291*, 253. (b) Dow Patent, U.S. 2004/0176629, 2004. (c) Bayer, A. G. Patent Appl. WO200158887, 2001.

(336) Min, B. K.; Friend, C. M. *Chem. Rev.* **2007**, *107*, 2709.

(337) Deng, X. Y.; Min, B. K.; Liu, X. Y.; Friend, C. M. *J. Phys. Chem. B* **2006**, *110*, 15982.

(338) Okumara, M.; Haruta, M.; Kitagawa, Y.; Yamaguchi, K. *Gold Bull.* **2007**, *40/1*, 40.

(339) Weiher, N.; Beesley, A. M.; Tsapatsaris, N.; Delannoy, L.; Louis, C.; van Bokhoven, J. A.; Schroeder, S. L. M. *J. Am. Chem. Soc.* **2007**, *129*, 2240.

(340) Chowdhury, B.; Bravo-Suárez, J. J.; Mimura, N.; Lu, J.; Bando, K. K.; Tsubota, S.; Haruta, M. *J. Phys. Chem. B* **2006**, *110*, 22995.

(341) Chowdhury, B.; Bravo-Suárez, J. J.; Daté, M.; Tsubota, S.; Haruta, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 412.

(342) Lu, J.; Zhang, X.; Bravo-Suárez, J. J.; Tsubota, S.; Gaudet, J.; Oyama, S. T. *Catal. Today* **2007**, *123*, 189.

(343) Nijuis, T. A.; Weckhuysen, B. M. *Catal. Today* **2006**, *117*, 84.

(344) Dai, M. H.; Tang, D. L.; Lin, Z. J.; Yang, H. W.; Yuan, Y. Z. *Chem. Lett.* **2006**, *35*, 878.

(345) Siinha, A. K.; Seelan, S.; Tsubota, S.; Haruta, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1546.

(346) Lu, J.; Zhang, X.; Bravo-Suárez, J. J.; Bando, K. K.; Fujitani, T.; Oyama, S. T. *J. Catal.* **2007**, *250*, 350.

(347) Sacaliuc, E.; Beale, A. M.; Weckhuysen, B. M.; Nijhuis, T. A. *J. Catal.* **2007**, *248*, 235.

(348) Hutchings, G. J.; Carrettin, S.; Landon, P.; Edwards, J. K.; Enache, D.; Knight, D. W.; Xu, Y.-J.; Carley, A. F. *Top. Catal.* **2006**, *38*, 223.

(349) Hughes, M. D.; Xu, Y.-J.; Jenkins, P.; McMorn, P.; Landon, P.; Enache, D. I.; Carley, A. F.; Attard, G. A.; Hutchings, G. J.; King, F.; Stitt, E. H.; Johnston, P.; Griffin, K.; Kiely, C. J. *Nature* **2005**, *437*, 1132.

(350) Pinnaduwage, D. S.; Zhou, L.; Gao, W.; Friend, C. M. *J. Am. Chem. Soc.* **2007**, *129*, 1872.

(351) (a) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (c) Mueller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (d) Hilt, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3586. (e) Aggarwal, V. K. *Synlett* **1998**, 329.

(352) (a) Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787. (b) Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005**, *7*, 3191. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (d) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (e) Man, W.-L.; Lam, W. W. Y.; Yiu, S.-M.; Lau, T.-C.; Peng, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 15336.

(353) (a) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (b) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202.

(354) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876.

(355) Deng, X.; Baker, T. A.; Friend, C. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7075.

(356) Karimi, B.; Biglari, A.; Clark, J. H.; Budaryn, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7210.

(357) (a) Yamada, Y. M. A.; Arakawa, T.; Hocke, H.; Uozumi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 704. (b) Karimi, B.; Abedi, S.; Clark, J. H.; Budarin, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 4766. (c) Stahl, S. S. *Science* **2005**, *309*, 1824.

(358) (a) Schmid, G., Ed. *Nanoparticles*; Wiley-VCH: Weinheim, Germany, 2004. (b) Sugimoto, T., Ed. *Fine Particles: Synthesis, Characterization and Mechanisms of Growth*; Marcel Dekker, New York, 2000. (c) Feldheim, D. L., Foss, C. A., Eds. *Metal Nanoparticles: Synthesis, Characterization and Applications*; Marcel Dekker: New York, 2002..

(359) Enache, D. I.; Knight, D. W.; Hutchings, G. J. *Catal. Lett.* **2005**, *103*, 43.

(360) (a) Milone, C.; Ingoglia, R.; Pistone, A.; Neri, G.; Galvagno, S. *Catal. Lett.* **2003**, *87*, 201. (b) Hayashi, T.; T. ; Inagaki, T. (Nippon Shokubai Co., Ltd., Japan)*PCT Int. Appl.* **2002**, 56. (c) Hayashi, T. (Nippon Shokubai Co., Ltd., Japan)*Jpn. Kokai Tokkyo Koho*, **2005**, 10.

(361) (a) Biella, S.; Rossi, M. *Chem. Commun.* **2003**, 378. (b) Carretin, S.; McMorn, P.; Johnston, P.; Griffin, K.; Kiely, C.; Attard, G. A.; Hutchings, G. J. *Top. Catal.* **2004**, *27* (1−4), 131. (c) Carretin, S.; McMorn, P.; Johnston, P.; K; Griffin, K.; Hutchings, G. J. *Chem. Commun.* **2002**, 696. (d) Biella, S.; Castiglioni, G. L.; Fumagalli, C.; Prati, L.; Rossi, M. *Catal. Today* **2002**, *72*, 43.

(362) Comotti, M.; Pina, C. D.; Matarrese, R.; Rossi, M. *Angew. Chem.* **2004**, *43*, 5812.

(363) Abad, A.; Concepcion, P.; Corma, A.; Garcia, H. *Angew. Chem.* **2005**, *44*, 4066.

(364) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362.

(365) Abad, A.; Almela, A.; Corma, A.; García, H. *Chem. Commun.* **2006**, 3178.

(366) Abad, A.; Corma, A.; García, H. *Pure Appl. Chem.* **2007**, *79*, 1847.

(367) (a) Mori, K; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 10657. (b) Yamaguchi, K.; Mizuno, N. *Chem.—Eur. J.* **2003**, *9*, 4353. (c) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037. (d) Musawir, M.; Davey, P. N.; Kelly, G.; Kozhevnikov, I. V. *Chem. Commun.* **2003**, 1414.

(368) Choudhary, V. R.; Jha, R.; Jana, P. *Green Chem.* **2007**, *9*, 267.

(369) Biffis, A.; Cunial, S.; Spontoni, P.; Prati, L. *J. Catal.* **2007**, *251*, 1.

(370) Dimitratos, N.; Lopez-Sanchez, J. A.; Morgan, D.; Carley, A.; Prati, L.; Hutchings, G. J. *Catal. Today* **2007**, *122*, 317.

(371) Enache, D. I.; Barker, D.; Edwards, J. K.; Taylor, S. H.; Knight, D. W.; Carley, A. F.; Hutchings, G. J. *Catal. Today* **2007**, *122*, 407.

(372) Haider, P.; Baiker, A. *J. Catal.* **2007**, *248*, 175.

(373) Kimmerle, B.; Grunwaldt, J.-D.; Baiker, A. *Top. Catal.* **2007**, *44*, 285.

(374) (a) Maddanimath, T.; Kumar, A.; D'Arcy-Gall, J.; Ganesan, P. G.; Vijayamohanan, K.; Ramanath, G. *Chem. Commun.* **2005**, 1435. (b) Ramanath, G.; DKArcy-Gall, J.; Maddaninath, T.; Ellis, A. V.; Ganesan, P. G.; Goswami, R.; Kumar, A.; Vijayamohanan, K. *Langmuir* **2004**, *20*, 5583. (c) Kumar, A.; Mandal, S.; Mathew, S. P.; Selvakannan, P. R.; Mandale, A. B.; Chaudhari, R. V.; Sastry, M. *Langmuir* **2002**, *18*, 6478.

(375) Miyamura, H.; Matsubara, R.; Miyazaki, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4151.

(376) (a) Aoshima, S.; Yoshida, T.; Kanazawa, A.; Kanaoka, S. *J. Polym. Sci. Part A: Polym. Chem.* **2007**, *45*, 1801. (b) Shibata, T.; Kanaoka, S.; Aoshima, S. *J. Am. Chem. Soc.* **2006**, *128*, 7497. (c) Sugihara, S.; Hashimoto, K.; Okabe, S.; Shibayama, M.; Kanaoka, S.; Aoshima, S. *Macromolecules* **2004**, *37*, 336.

(377) Kanaoka, S.; Yagi, N.; Fukuyama, Y.; Aoshima, A.; Tsunoyama, H.; Tsukuda, T.; Sakura, H. *J. Am. Chem. Soc.* **2007**, *129*, 12060.

(378) Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004.

(379) Li, H.; Guan, B.; Wang, W.; Xing, D.; Fang, Z.; Wan, X.; Yang, L.; Shia, Z. *Tetrahedron* **2007**, *63*, 8430.

(380) Hayashi, T.; Inagaki, T.; Itayama, N.; Baba, H. *Catal. Today* **2006**, *117*, 210.

(381) Prati, L.; Rossi, M. *J. Catal.* **1998**, *176*, 552.

(382) Mertens, P. G. N.; Vankelecom, I. F. J.; Jacobs, P. A.; De Vos, D. E. *Gold Bull.* **2005**, *38/4*, 157.

(383) Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Della Pina, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 4434.

(384) (a) Ketchie, W. C.; Murayama, M.; Davis, R. J. *Top. Catal.* **2007**, *44*, 307. (b) Porta, F.; Prati, L. *J. Catal.* **2004**, *224*, 397. (c) Carrettin, S.; McMorn, P.; Johnston, P.; Griffin, K.; Hutchings, G. J. *Chem. Commun.* **2002**, 696.

(385) Ketchie, W. C.; Fang, Y.-L.; Wong, M. S.; Murayama, M.; Davis, R. J. *J. Catal.* **2007**, *250*, 94.

(386) Dimitratos, N.; Lopez-Sanchez, J. A.; Lennon, D.; Porta, L.; Prati, L.; Villa, A. *Catal. Lett.* **2006**, *108*, 147.

(387) Ketchie, W. C.; Murayama, M.; Davis, R. J. *Top. Catal.* **2007**, *44*, 307.

(388) Dimitratos, N.; Villa, A.; Bianchi, C. L.; Prati, L.; Makkee, M. *Applied Catal. A: General* **2006**, *311*, 185.

(389) Demirel, S.; Kern, P.; Lucas, M.; Claus, P. *Catal. Today* **2007**, *122*, 292.

(390) Sinfelt, J. H. *Bimetallic Catalysts*; Wiley: New York, 1983.

(391) (a) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, M; Watanabe, A. A.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362. (b) Dimitratos, N.; Lopez-Sanchez, J. A.; Lennon, D.; Porta, F.; Prati, L.; Villa, A. *Catal. Lett.* **2006**, *108*, 147. (c) Dimitratos, N.; Villa, A.; Wang, D.; Porta, F.; Su, D.; Prati, L. *J. Catal.* **2006**, *244*, 113. (d) Wang, D.; Villa, A.; Porta, F.; Su, D.; Prati, L. *Chem. Commun.* **2006**, 1956. (e) Dimitratos, N.; Prati, L. *Gold Bull.* **2005**, *38*, 73. (f) Bianchi, C. L.; Canton, P.; Dimitratos, N.; Porta, F.; Prati, L. *Catal. Today* **2005**, *102−103*, 203.

(392) Ketchie, W. C.; Murayama, M.; Davis, R. J. *J. Catal.* **2007**, *250*, 264.

(393) Dimitratos, N.; Porta, F.; Prati, L. *Appl. Catal. A: General* **2005**, *291*, 210–214.

(394) Prati, L.; Villa, A.; Porta, F.; Wang, D.; Su, D. *Catal. Today* **2007**, *122*, 386.

(395) Abbadi, A.; Gotlieb, K. F.; Meiberg, J. B. M.; van Bekkum, H. *Appl. Catal. A: General* **1997**, *156*, 105.

(396) Venkin, M.; Touillaux, R.; Ruiz, P.; Delmon, B.; Devillers, M. *Appl. Catal. A: General* **1996**, *148*, 181.

(397) Biella, S.; Prati, L.; Rossi, M. *J. Catal.* **2002**, *206*, 242.

(398) Comotti, M.; Della Pinna, C.; Matarrese, R.; Rossi, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5812.

(399) Beltrame, P.; Comotti, M.; Della Pina, C.; Rossi, M. *Appl. Catal. A: General* **2006**, *297*, 1.

(400) Beltrame, P.; Comotti, M.; Della Pina, C.; Rossi, M. *J. Catal.* **2004**, *228*, 282.

(401) Comotti, M.; Della Pina, C.; Falletta, E.; Rossi, M. *Adv. Synth. Catal.* **2006**, *348*, 313.

(402) Barton, D. G.; Podkoizin, S. G *J. Phys. Chem.* **2005**, *109*, 2262.

(403) (a) Baatz, C.; Thielecke, N.; Prüβe, U. *Appl. Catal. B: Environ.* **2007**, *70*, 653. (b) Mirescu, A.; Prüsse, U. *Catal. Commun.* **2006**, *7*, 11.

(404) Thielecke, N.; Aytemir, M.; Prüsse, U. *Catal. Today* **2007**, *121*, 115.

(405) Baatz, C.; Prüβe, U. *J. Catal.* **2007**, *249*, 34.

(406) Baatz, C.; Prüβe, U. *Catal. Today* **2007**, *122*, 325.

(407) Mirescu, A.; Berndt, H.; Martin, A.; Prüβe, U. *Appl. Catal. A: General* **2007**, *317*, 204.

(408) Mirescu, A.; Prüβe, U. *Appl. Catal.B: Environ.* **2007**, *70*, 644.

(409) Zhu, B.; Angelici, R. J. *Chem. Commun.* **2007**, 2157.

(410) Della Pinna, C.; Falletta, E.; Rossi, M. *Top. Catal.* **2007**, *44*, 325.

(411) Hawker, C. J. *Trends Polym. Sci.* **1996**, *4*, 83.

(412) Lazar, M; Angelici, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 10613.

(413) (a) Ontko, A. C.; Angelici, R. J. *Langmuir* **1998**, *14*, 3071. (b) Ontko, A. C.; Angelici, R. J. *Langmuir* **1998**, *14*, 1684. (c) Shih, K.-C.; Angelici, R. J. *Langmuir* **1995**, *11*, 2539. (d) Robertson, M. J.; Angelici, R. J. *Langmuir* **1994**, *10*, 1488.

(414) Michelin, R. A.; Pombeiro, A. J. L; Guedes da silva, M. F. *Coord. Chem. Rev.* **2001**, *218*, 75.

(415) Bonati, F.; Minghetti, T. J. *Organomet. Chem.* **1973**, *59*, 403.

(416) (a) Parks, J. E. J. *Organomet. Chem.* **1974**, *71*, 453. (b) Minghetti, G.; Bonati, F.; Banditelli, G. *Inorg. Chem.* **1976**, *15*, 1718.

(417) Zhu, B.; Angelici, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 14460.

(418) (a) McReynolds, D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (b) Zeni, G.; Larock, R. C. *Chem. Rev* **2004**, *104*, 2285.

(419) de Bruin, B.; Budzelaar, P. H. M.; Gal, A. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4142.

(420) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.

(421) Liu, Y.; Song, F.; Guo, S. J. *Am. Chem. Soc.* **2006**, *128*, 11332.

(422) Taduri, B. P.; Sohel, S. A.; Cheng, H.-M.; Lin, G.-Y.; Liu, R.-S. *Chem. Commun.* **2007**, 2530.

CR068435D