CHEMISTRY
AN ASIAN JOURNAL

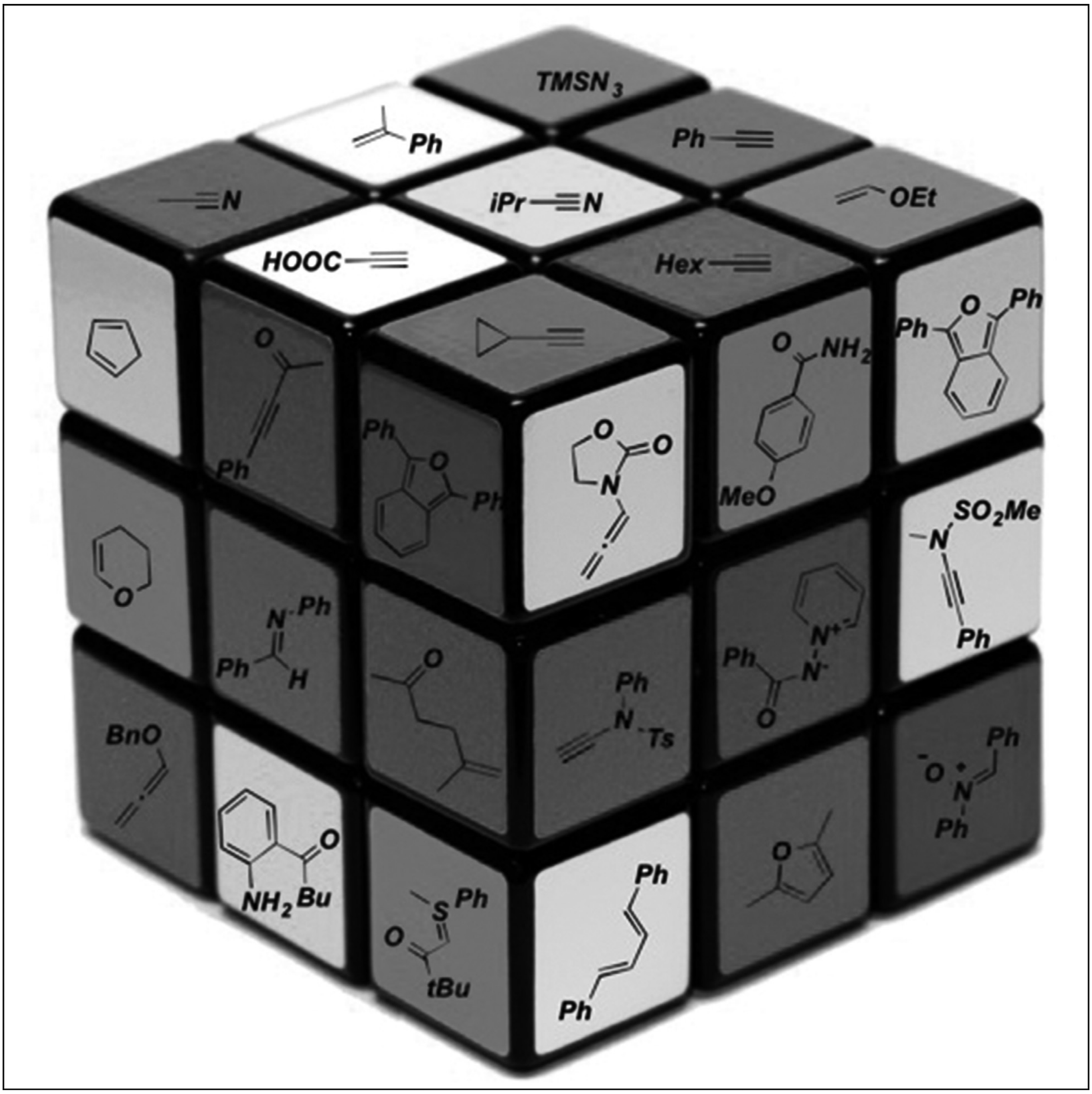
ACES

FOCUS REVIEW

DOI: 10.1002/asia.201402395

Meeting the Challenge of Intermolecular Gold(I)-Catalyzed Cycloadditions of Alkynes and Allenes

Michael E. Muratore,[a] Anna Homs,[a] Carla Obradors,[a] and Antonio M. Echavarren*[a, b]



Abstract: The development of gold(I)-catalyzed intermolecular carbo- and hetero-cycloadditions of alkynes and allenes has been more challenging than their intramolecular counterparts. Here we review, with a mechanistic perspective, the most fundamental intermolecular cycloadditions of alkynes and allenes with alkenes.

Keywords: alkynes • allenes • cycloaddition • gold

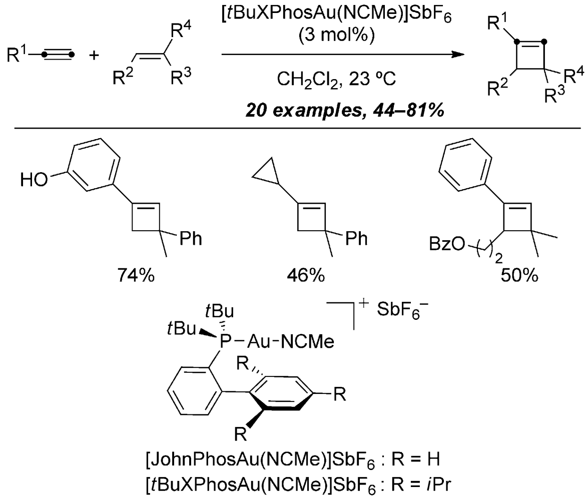
1. Introduction

The development of gold(I)-catalyzed reactions relied on intramolecular reactions of 1,n-enynes and their allene analogues.[1,2] Much less attention was given initially to the corresponding intermolecular reactions, which, in principle, are more challenging. In an intermolecular process involving two unsaturated substrates, their possible competitive binding with the gold complex should be considered,[3] as well as the fact that gold catalysts are inherently acidic and therefore can promote the polymerization of alkenes by cationic mechanisms.[4] Nevertheless, in the last few years a number of intermolecular cycloadditions with significant synthetic potential have been discovered. Herein, we review the most fundamental intermolecular reactions of alkynes and allenes with alkenes that lead to the formation of cyclic compounds.

It is important to remark that in gold(I) chemistry, ligand substitutions usually occur by associative mechanisms in which AuL^+ species are not formed.[5,6] Here, for the sake of simplicity, "AuL^+" is used in mechanistic schemes as a surrogate for cationic 14-electron $[AuLL']^+$ complexes, where L′ is a relatively weakly bound substrate (alkyne, allene, or alkene), product, or donor solvent molecule.

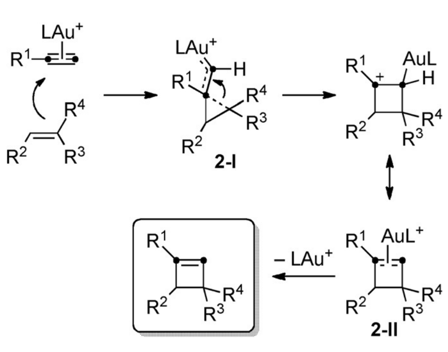
2. Cycloadditions of Alkynes

The first intermolecular cycloaddition catalyzed by gold(I) involved electron-rich alkynes and alkenes that reacted to form regioselectively cyclobutenes (Scheme 1),[7] which are useful building blocks in synthesis.[8] This reaction required the use of sterically hindered gold(I) complex [*t*BuXPhosAu(NCMe)]SbF_6 as catalyst, a member of a family of highly reactive cationic gold(I) complexes such as [JohnPhosAu(NCMe)]SbF_6, which circumvent the addition of any silver salt to catalyze a wide range of synthetically useful transformations.[1m,9] The reaction required arylacetylenes, although cyclopropylacetylene could also be used. However, internal alkynes such as 1-phenyl-1-propyne and 1-phenyl-1-hexyne were recovered unchanged under these conditions. Regarding the alkene counterparts, di- and trisubstituted olefins took part efficiently in this transformation. An intramolecular version of this transformation led to the preparation of large ring macrocycles.[10]



Scheme 1. Gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes and alkenes.

The [2+2] cycloaddition probably proceeds by electrophilic addition of the π-gold(I)–acetylene complex to the alkene to form cyclopropyl gold(I)–carbene intermediate (**2-I**), analogous to that proposed in the cycloisomerizations of 1,n-enynes with gold(I) (Scheme 2).[1,2] These intermediates



Scheme 2. Mechanistic proposal for the formation of cyclobutenes.

[a] Dr. M. E. Muratore, A. Homs, C. Obradors, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: aechavarren@iciq.es

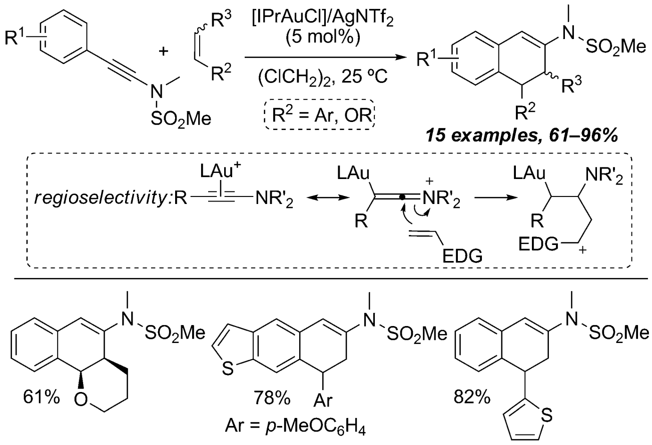
[b] Prof. A. M. Echavarren
Departament de Química Analítica i Química Orgànica
Universitat Rovira i Virgili
C/Marcel·lí Domingo s/n, 43007 Tarragona (Spain)

could then undergo ring expansion to form a stabilized tertiary carbocation and finally the cyclobutene after demetalation (Scheme 2).

Density functional theory (DFT) calculations have shown that (**2-I**) is a highly distorted species between a cyclopropyl gold(I)–carbene and a gold(I)-stabilized homoallylic carbocation,[2g,h] with cyclopropane bond lengths from 1.44 to 1.71 Å.[11] The structure of the key intermediates in the cycloisomerizations of 1,5-enynes was also found to be highly delocalized.[2i]

The regioselective formation of intermediate (**2-II**) was explained by analogy with the *exo*-type intermediates proposed for the gold(I)-catalyzed cyclization of 1,n-enynes, which is usually the most favored pathway.[2] Deuteration experiments showed that the free rotation of cyclopropyl intermediate (**2-I**) does not occur except when the alkene bears an aryl substituent. Furthermore, the gold(I)–carbene could be trapped intermolecularly with another alkene by cyclopropanation.[12]

Further studies allowed the development of the [4+2] annulation of arylynamides with alkenes (Scheme 3).[13] Opti-



Scheme 3. Gold(I)-catalyzed [4+2] cycloaddition between arylynamides and alkenes.

mal results were observed when employing the electron-donating carbene (IPr)-bound gold(I) catalyst associated to the more coordinating triflimide counteranion in chlorinated solvents. The reaction proceeded smoothly in excellent yields with electron-rich alkenes and with different substituents on the aromatic ring such as fluoro, chloro, methoxy, hydroxyl, or thiol. The regioselectivity of this reaction was explained by the initial attack of the electron-rich alkene to the electrophilic arylynamide–gold(I) complex.

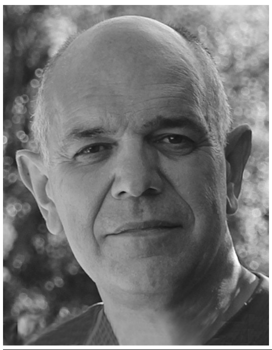
This reaction presumably follows a pathway analogous to the [2+2] cycloaddition between alkynes and alkenes, through a cyclopropyl gold(I)–carbene, followed by a Friedel–Crafts reaction and protodemetalation (Scheme 4). When an enol ether was used, elimination of the corresponding alcohol occurred, leading to the aromatization of the final product.

By contrast, when a terminal ynamide and an enol ether were treated with a gold complex with a bulky phosphine ligand, an intermolecular [2+2+2] reaction took place

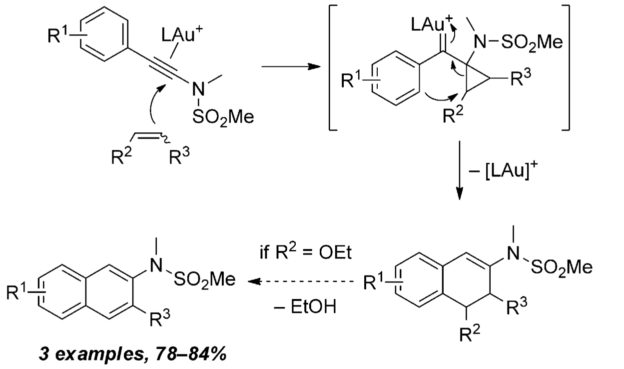
Michael E. Muratore was born in Grasse (France) in 1983. He studied at the University of Nice-Sophia Antipolis (B.Sc.) and at the Ecole National Supérieure de Chimie de Montpellier (ENSCM) where he graduated in 2007 (M.Sc.). After completing his PhD under the supervision of Prof. Dr. Darren J. Dixon at the University of Oxford (UK) in 2011, he spent 18 months in the research group of Prof. Dr. Magnus Rueping at RWTH Aachen (Germany) as a postdoctoral fellow. In 2013, he joined the research group of Prof. Dr. Antonio M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ) as a postdoctoral research assistant.

Anna Homs was born in Igualada (Barcelona) in 1986. After completing her B.Sc. in Chemistry (2009) at the Institut Químic de Sarrià (Barcelona), she moved to Germany, where she carried her diploma thesis at Bayer CropScience A.G. Since 2010 she is a PhD student at the Institute of Chemical Research of Catalonia (ICIQ) working under the supervision of Prof Dr. Antonio M. Echavarren.

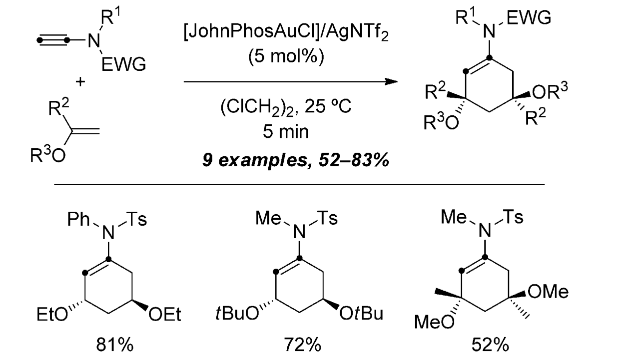
Carla Obradors was born in Manresa (Barcelona) in 1987. She graduated in Chemistry at Universitat Autònoma de Barcelona in 2010. Meanwhile, she also worked at Parc Científic de Barcelona and Institut de Química Avançada de Catalunya (CSIC). In 2011, she was awarded the Master of Synthesis and Catalysis Extraordinary Prize at Universitat Rovira i Virgili (Tarragona). Since 2011, she is carrying out her PhD studies under the supervision of Prof. Dr. Antonio M. Echavarren at the Institut of Chemical Research of Catalonia (ICIQ).



Antonio M. Echavarren obtained his PhD at the Universidad Autónoma de Madrid (UAM) in 1982. After postdoctoral stays at Boston College and Colorado State University, he joined the CSIC (Institute of Organic Chemistry) in Madrid. In 1992 he became Professor of Organic Chemistry at the UAM. He is also Professor of Research at the CSIC. In 2004 he moved to Tarragona as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ).



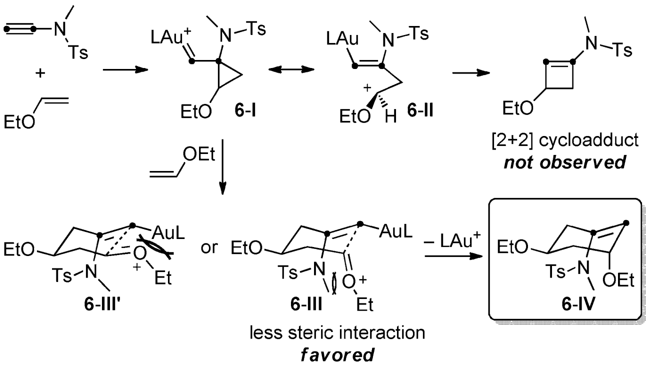
Scheme 4. Proposed mechanism for the formal [4+2] cycloaddition of arylynamides and alkenes—cyclopropylgold(I)–carbene formation/Friedel–Crafts domino sequence, and elimination towards 2-aminonaphthalene derivatives.



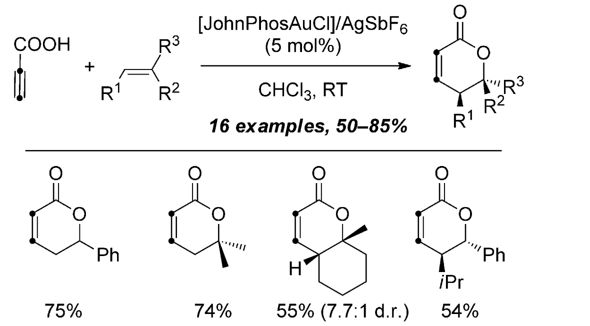
Scheme 5. Gold(I)-catalyzed [2+2+2] cycloaddition of terminal ynamides and enol ethers.

(Scheme 5).[13] In this case, several substituents on the ynamide group (EWG = methanesulfonyl, toluenesulfonyl, or phenylsulfonyl; R^1 = *n*-butyl, benzyl, or phenyl) and on the alkoxyethene (R^2 = H, Me; R^3 = Me, Et, *t*Bu) were tolerated, leading to the final product diastereoselectively.

[2+2] Cycloadducts were not observed, which indicates that the attack of a second molecule of enol ether is faster



Scheme 6. Mechanistic rationale for the observed diastereoselective [2+2+2] cycloaddition between a terminal ynamide and enol ethers—cyclopropylgold(I)–carbene formation/2nd alkene reaction/oxonium cyclization towards *N*,*N*-disubstituted cyclohexenamines.

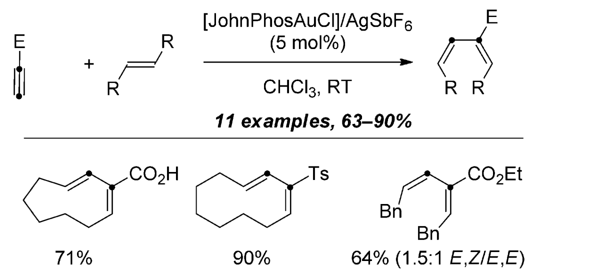


Scheme 7. Gold(I)-catalyzed [4+2] cycloaddition between carboxylic acids and alkenes.

than the ring expansion of the cyclopropyl gold–carbene (**6-I**/**6-II**) required for the [2+2] cycloaddition (Scheme 6). The authors postulated the formation of a more sterically favored oxonium intermediate (**6-III**), which leads to cyclohexenamine (**6-IV**).

A [4+2] cycloaddition between propargylic esters or carboxylic acids and alkenes was also developed to build α,β-unsaturated lactones (Scheme 7).[14] In this case, a gold(I) complex bearing the bulky JohnPhos ligand was the catalyst of choice.

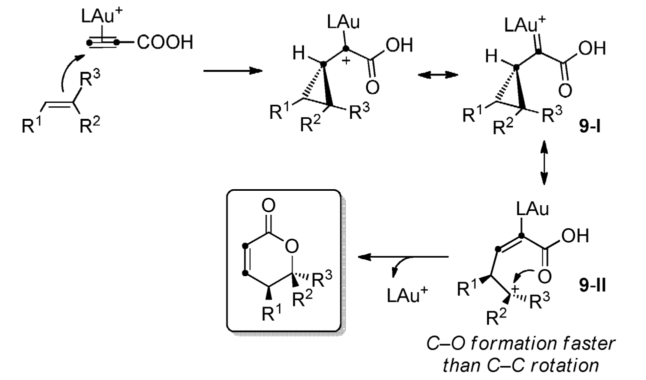
1,1-Disubstituted alkenes tolerating silyl groups and ethers on the pendant chain, trisubstituted alkenes, 1,3-dienes, and allenes could be used as reaction partners. Surprisingly, when 1,2-disubstituted alkenes were used, 1,3-dienes were formed stereospecifically by a metathesis-like process (Scheme 8).[14] *cis*-Substrates gave *E,E*-products and



Scheme 8. Gold(I)-catalyzed enyne metathesis between carboxylic acids and 1,2-disubstituted alkenes.

trans-precursors gave *E,Z*-dienes exclusively, whereas nonsymmetrical substrates reacted with poor regioselectivity.

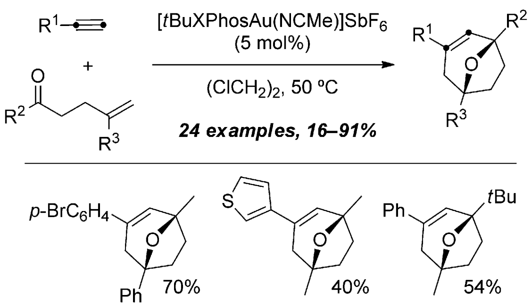
According to DFT calculations, both the [4+2] cycloaddition and the 1,3-diene synthesis proceed through the formation of cyclopropylgold(I)–carbene (**9-I**) (Scheme 9).[14] In contrast with the previous studies, the alkyne internal carbon becomes the carbene center in this type of substrates. The cyclization of the carboxylate could be a stepwise process (through a gold-stabilized homoallylic carbocation (**9-II**)); however, the overall cycloaddition is stereospecific, which demonstrates that the C–O bond formation occurs faster than the possible C–C bond rotation on the homoallyl carbocation. In addition, 65% *ee* was obtained



Scheme 9. Proposed reaction pathway for the formation of α,β-unsaturated lactones—cyclopropylgold(I)–carbene formation/lactonization sequence.

when the reaction was performed with (*R*)-DM-SEGPHOS as a ligand, constituting the first example of a direct asymmetric intermolecular cycloaddition between alkynes and alkenes. A mechanism featuring a σ-bond rearrangement was proposed for the enyne metathesis. The formation of a cyclobutene that underwent ring opening was discarded due to the disagreement between the observed stereoselectivity and the one predicted according to the torquoelectronic effect.[15]

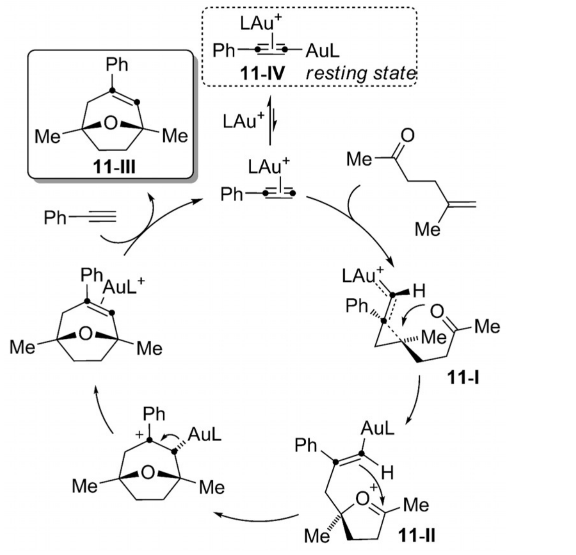
An intermolecular [2+2+2] cycloaddition cascade between alkynes and oxoalkenes has also been developed (Scheme 10).[16] Analogously to the cyclization used to form the core of (+)-orientalol F[17] and (−)-englerin A,[18] [3.2.1]-oxabicycles were readily built under mild conditions. In this



Scheme 10. Intermolecular [2+2+2] cycloaddition between alkynes and oxoalkenes.

case, the best results were obtained using [*t*BuXPhosAu(NCMe)]SbF_6 as a catalyst. The cycloaddition proceeded with a variety of arylacetylenes bearing *ortho*, *meta*, and *para* electron-donating or electron-withdrawing substituents. Hetero- and polyaromatic rings were also tolerated as well as different alkyl and aryl groups at the α-position of the ketone and on the alkene moiety. In a few cases, the formation of tetrahydrofurans as side-products was also observed.

The formation of the cyclopropylgold(I)–carbene (**11-I**) was again suggested as the first step of the intermolecular [2+2+2] cycloaddition, followed by the regioselective nucleophilic attack of the carbonyl (Scheme 11).[16] The oxonium

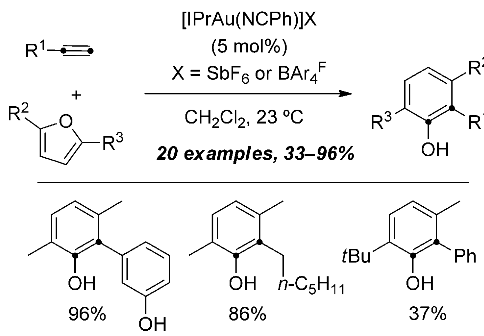


Scheme 11. Cascade process for the formation of oxabicycles—cyclopropylgold(I)–carbene formation/oxy-cyclization/Prins-type reaction sequence.

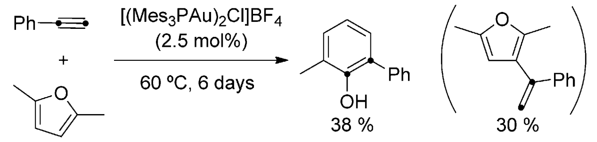
cation (**11-II**) could then undergo a Prins-type cyclization and finally demetalation to afford the oxabicyclic products (**11-III**). Although the mechanistic proposal was supported by DFT calculations and deuterium labeling experiments, monitoring of the reaction by ^{1}H and ^{31}P NMR spectroscopies showed a more complicated scenario, in which a σ,π-digold complex **11-IV** was proposed to be the resting state of the system.[16] This dinuclear complex acted as a dead-end, capturing most of the active gold(I) and decreasing the reaction rate. Similar digold(I) complexes have been obtained in other contexts.[19]

The formation of less reactive σ,π-digold complexes such as **11-IV** requires the deprotonation of the active π-gold(I)–acetylene complexes. Therefore, for the development of efficient intermolecular reactions involving terminal alkynes, the use of a more bulky, non-coordinating, and less basic counteranion could have a significant beneficial effect by slowing down the formation of σ,π-digold complexes.[20] This effect was demonstrated in the intermolecular formation of phenols by reaction of furans with alkynes (Scheme 12).[21]

A single example of this intermolecular phenol synthesis had been reported before using the Schmidbauer–Bayer bi-



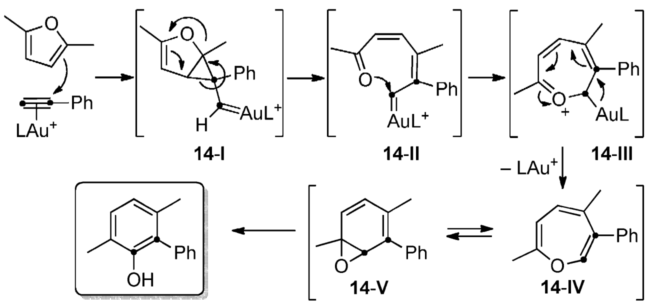
Scheme 12. Gold(I)-catalyzed cycloaddition of furans and alkynes.



Scheme 13. Intermolecular precedent of the formation of phenols.

nuclear gold(I) complex $[(Mes_3PAu)_2Cl]BF_4$ as a catalyst, and the reaction required 6 days to complete under neat conditions (Scheme 13).[22]

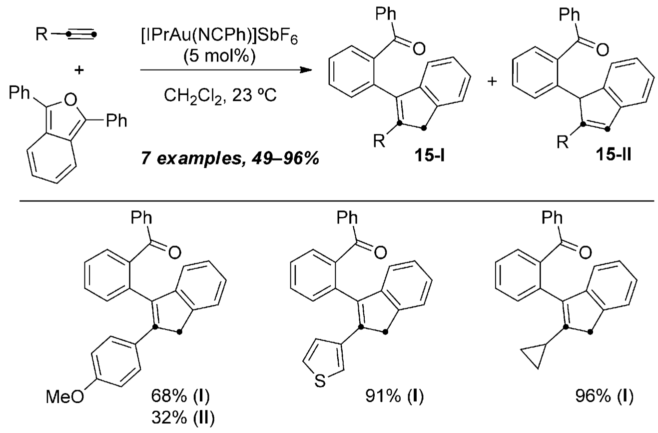
The application of NHC ligands combined with BAr_4^{F-} as counteranion remarkably improved the outcome of the procedure.[21] The scope was expanded to substituted aromatic rings with electron-donating and electron-withdrawing groups as well as aliphatic alkynes. Non-symmetrical furans were also used, leading to phenols with moderate to good regioselectivities. This phenol synthesis proceeds through a complex mechanism based on the formation of a cyclopropylgold(I)–carbene (**14-I**) between the activated alkyne and the furan, followed by ring opening to form a new gold(I)–carbene (**14-II**) that cyclizes to generate an oxonium cation (**14-III**). Elimination of gold(I) generates an oxepin (**14-IV**), which is in tautomeric equilibrium with an arene oxide (**14-V**). Phenols are finally obtained by opening of this epoxide (Scheme 14).[23]



Scheme 14. Mechanistic proposal for the phenol synthesis—cyclopropylgold(I)–carbene formation/oxy-cyclization/oxepin-arene oxide formation/epoxide opening sequence.

Interestingly, the reaction of 1,3-diphenylisobenzofuran with terminal alkynes led to disubstituted indenes (Scheme 15).[21] In this case, the intermediate gold(I)–carbene (similar to (**14-II**), Scheme 14) reacts by a Friedel–Crafts-type process with a phenyl ring, leading to the indene.

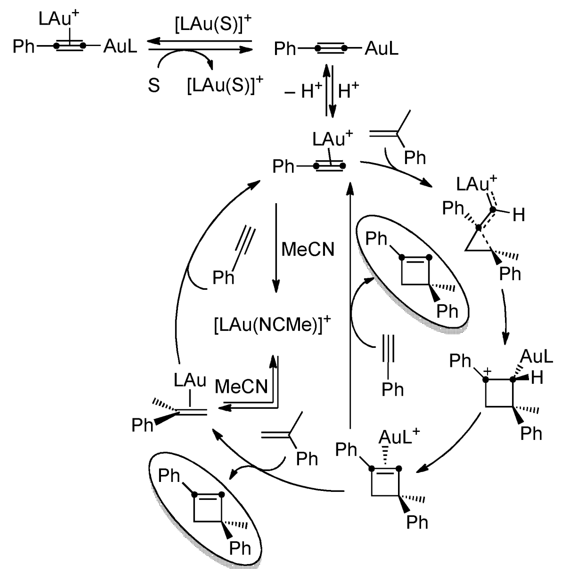
A detailed study on the role of the catalyst counterion was performed in the context of gold(I)-catalyzed intermolecular reactions.[20] Catalysts bearing NHC or phosphine ligands in combination with BAr_4^{F-} as the counteranion were found to impart the highest reactivity. Thus, the cyclobutene formation by [2+2] cycloaddition was improved (yields increased by 10–30%) and the scope of the reaction was expanded to acetylenes substituted with heteroaromatic rings and *ortho*-substituted arenes. Silyl groups, ethers, and silyl



Scheme 15. Formation of indenes by gold(I)-catalyzed cycloaddition of 1,3-diphenylisobenzofuran and alkynes.

ethers were now tolerated on the alkene partner. Moreover, the new catalysts also led to higher yields in the macrocyclization of 1,n-enynes ($n \geq 10$) and in the [2+2+2] cycloaddition of alkynes and oxoalkenes.

Kinetic studies together with low-temperature NMR experiments and determination of equilibrium constants revealed a complex system for the formation of the active catalytic species (Scheme 16).[20] Thus, the rate-determining



Scheme 16. Detailed mechanism of the gold(I)-catalyzed [2+2]-cycloaddition between alkynes and alkenes.

step of the process was determined to be the ligand exchange to form the π-alkyne–gold(I) complex, which could then undergo nucleophilic attack by the alkene or competitively be deprotonated to produce the unproductive σ,π-digold complex. Remarkably, when a bulkier and less basic counterion was used, the active species could be observed at up to 0 °C whereas with smaller anions it decomposed at −40 °C.

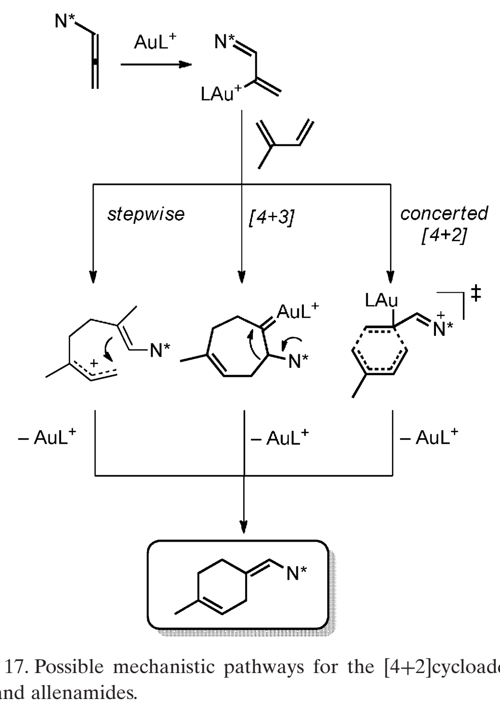
2. Cycloadditions of Allenes

Intramolecular gold-catalyzed cycloadditions of allene derivatives with 1,3-dienes[24] and alkenes[25] are well established and have been studied in detail over the past decade. However, the intermolecular counterpart has drawn little attention until recently, presumably due to the challenges posed by such reactivity. Generally, activated allenes are necessary to overcome both reactivity and regioselectivity issues. In this context, it is not surprising that the first study of a gold-catalyzed cycloaddition of allene derivatives and olefins was not reported until 2011. Over the past few years, several researchers have demonstrated the feasibility and illustrated the scope of [2+2]-, [3+2]-, [4+2]- and other types of cycloadditions with allenes.

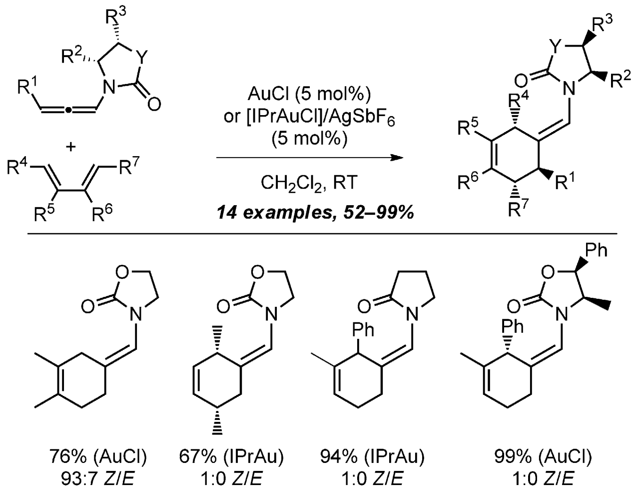
2.1. [4+2]-Cycloadditions of allenes and dienes

The first studies on gold-catalyzed cycloadditions of allenes and olefins described novel [4+2]-cycloadditions of allenamides[26]/allenyl ether[27] and 1,3-dienes towards the formation of cyclohexene derivatives bearing a pendant functionalized *exo*-olefin. Similarly to the intramolecular process, this intermolecular cycloaddition may proceed via three main pathways: a concerted [4+2]-pathway reminiscent of the Diels–Alder reaction, a concerted [4+3]-cycloaddition followed by ring contraction, and a stepwise path involving an allylic carbocation (Scheme 17).

Electronically neutral allenes did not react cleanly with 1,3-dienes under a variety of conditions. By contrast, electron-rich allenes such as allenamides are known to be easily accessible and reactive substrates in gold catalysis.[28] This observation was exploited in order to develop a novel intramolecular cycloaddition of allenamides with acyclic dienes. Although various electrophilic gold(I) catalysts promoted this transformation, simple AuCl (and alternatively [IPrAuCl]/$AgSbF_6$) proved to give superior results. Employing this catalytic system, the cyclohexene products were isolated in generally good yields and the competitive formation of the [2+2]-cycloadducts was kept to a minimum. Moreover, these conditions also provided the highest control for the *exo*-olefin geometry with a large preference for the (*Z*)-isomer. A range of 1,3-dienes partook in the cycloaddition: 2,3-dimethylbutadiene, 1,3-pentadiene, 2,4-hexadiene, and several other simple 1,3-dienes proved to be good reaction partners. Phenyl-substituted 1,3-dienes as well as an electron-rich enol ether generally afforded higher yields of the cycloadducts (Scheme 18).



Scheme 17. Possible mechanistic pathways for the [4+2]cycloaddition of dienes and allenamides.

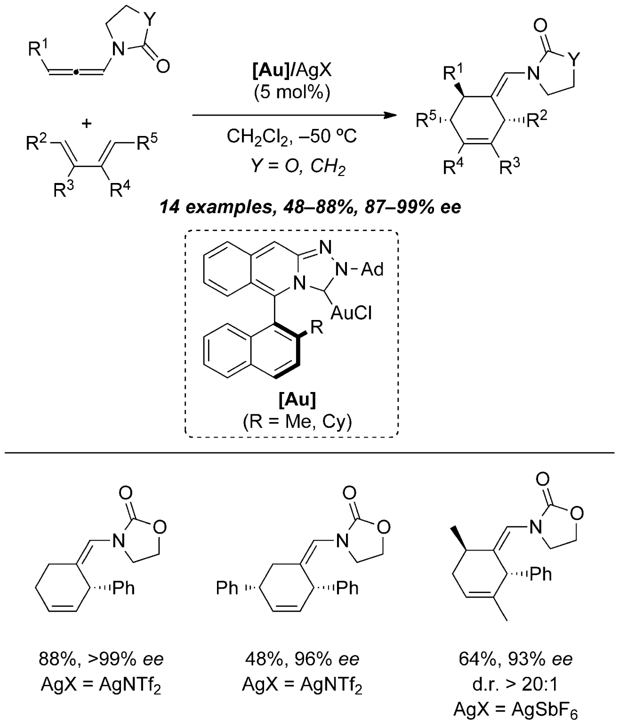


Scheme 18. Gold(I)-catalyzed [4+2]-cycloaddition of 1,3-dienes and allenamides/allenecarbamates.

Unsubstituted (terminal) or substituted (internal, chiral) allenyloxazolidinones reacted similarly in this transformation, the latter giving perfect diastereoselectivity. In addition, through the employment of a chiral oxazolidinone, the transformation showed excellent diastereoselectivity and great potential for the application to the synthesis of enantioenriched cyclohexene frameworks.[26]

The enantioselective version of this reaction was also developed employing newly designed axially chiral NHC ligands coordinated to gold(I). It is worth noting that with usual chiral NHC ligands, only low enantiomeric excess (*ee*) values were obtained whereas the newly developed ligands provided *ee* values generally over 90 % (Scheme 19).[29]

According to DFT studies, the reaction mechanism is highly dependent on the nature of the diene (enol ethers tend to react prominently via a stepwise pathway) and is also influenced by the nature of the catalyst. In most cases, several of the proposed mechanistic pathways may be operative and competitive in this transformation. However, the stereoselectivity of the reaction (*exo*-olefin geometry, diastereoselectivity) is accounted for by the energetically most fa-

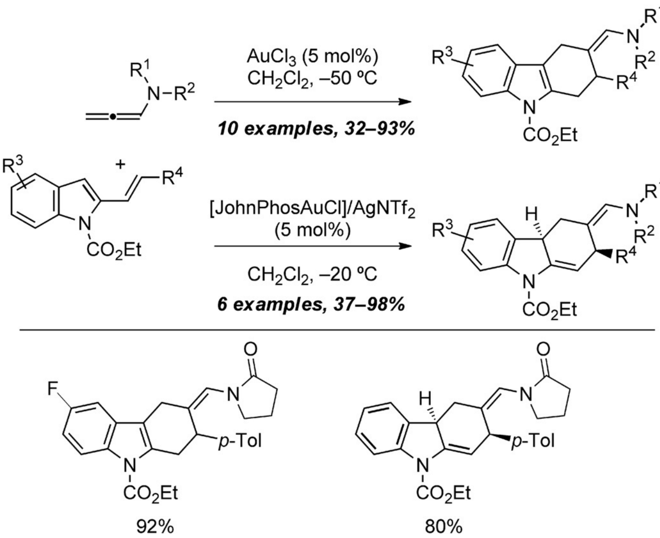


Scheme 19. Gold(I)-catalyzed enantioselective [4+2]-cycloaddition of 1,3-dienes and allenamides/allenecarbamates.

vorable transition state in all cases. The selectivity for the [4+2]-cycloadduct is also explained by an energetically more demanding pathway towards the [2+2] cycloadduct under AuCl catalysis (stepwise pathway). This is partially true for [IPrAuCl]/$AgSbF_6$ as a catalyst, and in this case the formation of the [2+2]-cycloadduct (cationic stepwise pathway), which is less energetically disfavored, becomes competitive. This explains why a significant amount of this by-product may be observed under these conditions.[30]

Simple 1,3-dienes are not the only substrates that react with allenamides through [4+2]-cycloaddition, but 2-vinyl indoles also take part in this type of transformation under gold catalysis. The protection of the indole nitrogen with a carbamate was critical in order to observe the cycloaddition. Interestingly, employing $AuCl_3$ or [JohnPhosAuNTf$_2$] as a catalyst selectively afforded two isomeric tetrahydrocarbazole derivatives. In addition, complete (*Z*)-selectivity of the olefin geometry was observed in all cases. Various β-aryl-substituted 2-vinylindoles were competent cycloaddition partners; however, alkyl-substituted 2-vinylindoles gave moderate yields, and only terminal allenamides were screened in this study (Scheme 20).[31]

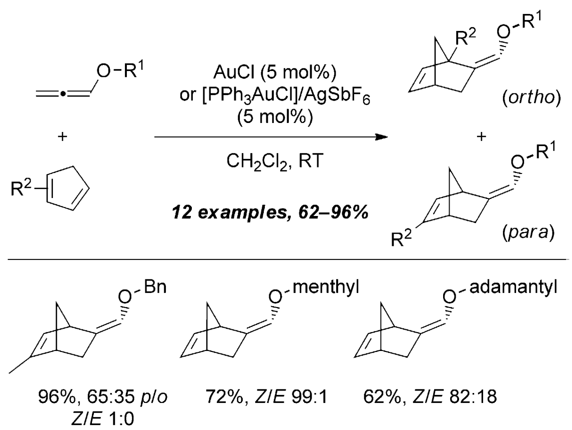
The [4+2]-cycloaddition of allenyl ethers and 1,3-dienes was also developed.[27] Gold catalysts, in particular a cationic gold(I) species ([PPh$_3$AuCl]/$AgSbF_6$), proved to be essential for the reactivity. $PtCl_2$, $PdCl_2$, $AgSbF_6$, and a range of strong Lewis acids were unable to promote this reaction. However, the same transformation was possible without catalyst at higher temperature. Interestingly, gold catalysis and thermal activation produced mainly the (*Z*)- and (*E*)-olefin



Scheme 20. Gold(I)-catalyzed [4+2]-cycloaddition of 2-vinylindoles and allenamides.

isomers, respectively, which makes these two methods complementary. Various terminal allenyl ethers and monosubstituted cyclopentadienes reacted to form bicyclo-[2.2.1]heptenes featuring pendant (*Z*)-enol ethers. Mixtures of bridgehead-substituted (*ortho*) and olefin-substituted (*para*) compounds were obtained in all cases (Scheme 21).

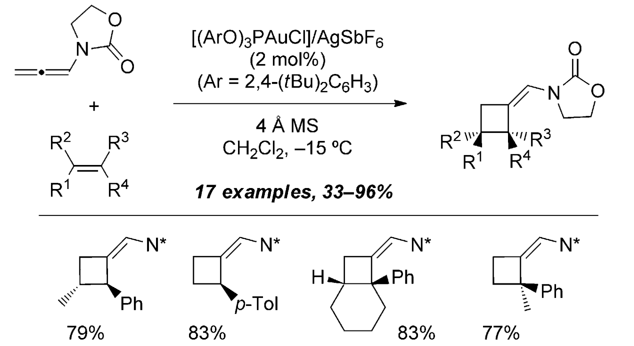
Substituted cyclopentadienes proved to be excellent reaction partners; however, the reactivity of acyclic 1,3-dienes was rather limited and poor to moderate yields of cyclohexenes were obtained, although the (*Z*/*E*) ratio remained equally high.



Scheme 21. Gold(I)-catalyzed [4+2]-cycloaddition of cyclopentadienes and allenyl ethers.

2.2. [2+2]-Cycloadditions of allenes and alkenes

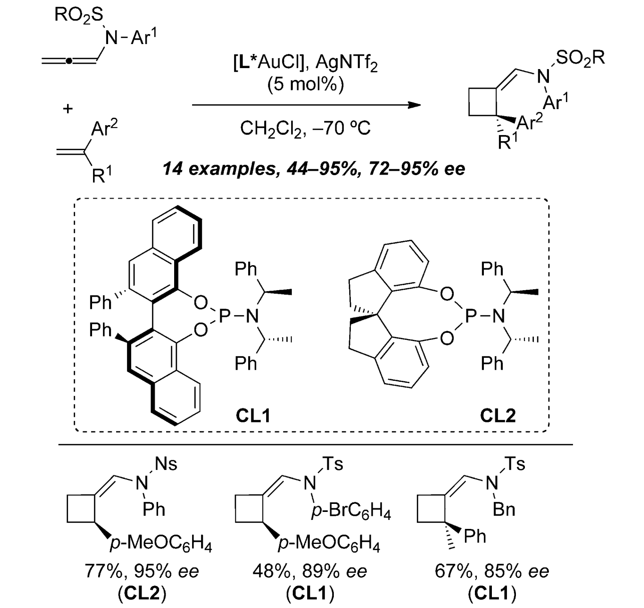
Taking advantage of the observation of a [2+2]-cycloaddition side-product in the reaction between allenamides/allenecarbamates and dienes, the [2+2]-cycloaddition of allenecarbamates and olefins towards the formation of decorated



Scheme 22. Gold(I)-catalyzed [2+2]-cycloaddition of activated olefins and allenecarbamates.

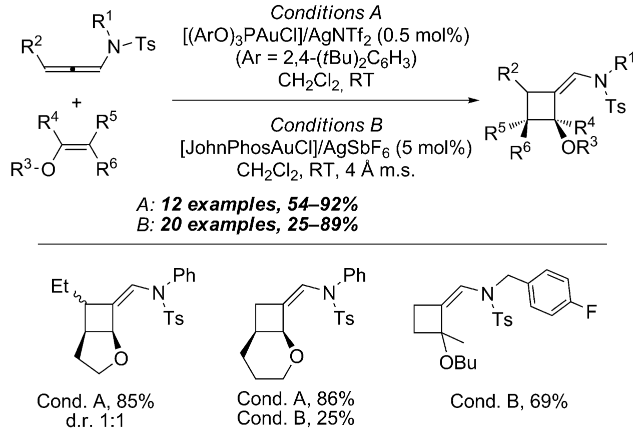
cyclobutanes was developed (Scheme 22).[32] A highly electrophilic cationic phosphite-bound gold catalyst gave the best results in this reaction. From a practical point of view, dropwise addition of the allenecarbamate cycloaddition partner over one hour was necessary to ensure good yields of cyclobutane adduct. Various styrene derivatives as well as enamides and enecarbamates proved to be excellent olefin partners. However, less activated olefins presented a poor reactivity. The scope with regard to the allene was not studied thoroughly, and only *N*-allenyloxazolidinone was subjected to this cycloaddition. Notably, this transformation also proceeded with complete diastereoselectivity and afforded the (*Z*)-*exo*-olefin isomer exclusively. Mechanistically, there is evidence that this cycloaddition takes place via a stepwise carbocationic pathway.

The cycloaddition with styrene derivatives was later rendered enantioselective by employing chiral phosphoramidite ligands. Ligands **CL1** and **CL2** generally gave good results.[33] With this approach, aryl-substituted cyclobutanes (bearing the methylene moiety) were synthesized with *ee* values ranging from 72 % to 95 % (Scheme 23).



Scheme 23. Gold(I)-catalyzed enantioselective [2+2]-cycloaddition of styrenes and allenesulfonamides.

The scope of the [2+2]-cycloadditions was expanded to other activated olefins, namely enol ethers (in particular dihydrofuran and tetrahydropyran). This strategy allows the construction of complex heterocycle-fused and functionalized cyclobutanes (Scheme 24).[34,35]



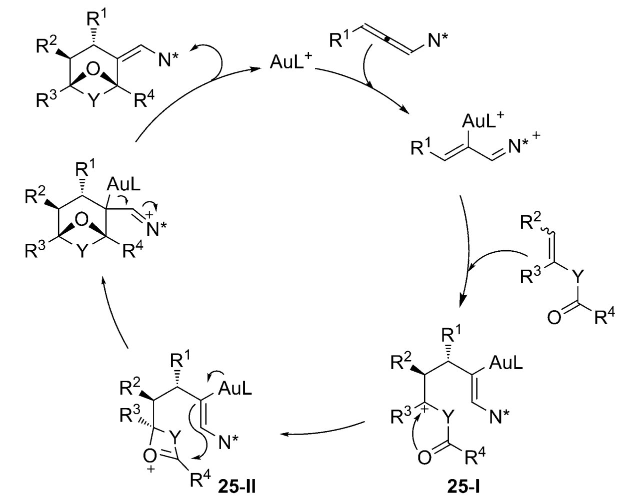
Scheme 24. Gold(I)-catalyzed [2+2]-cycloaddition of enol ethers and allenesulfonamides.

It is worth mentioning that allenamides may dimerize through a [2+2]-cycloaddition, which is usually considered as a side reaction.[32] However, it may lead to interesting functionalized bis methylenecyclobutanes.[34,35]

2.3. Other cycloadditions

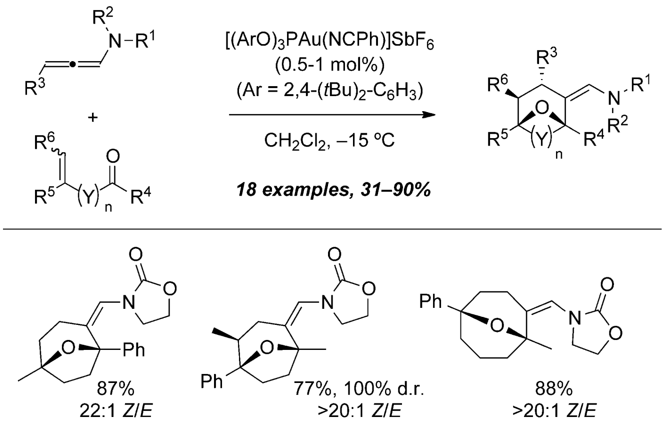
Although 1,6-dienes did not participate in a cycloaddition cascade with allenamides towards carbobicycles, as in the reaction with alkynes (Scheme 10),[16] oxoalkenes demonstrated to be excellent reaction partners in this type of cascade.[36] This strategy expanded the scope of gold-catalyzed intermolecular cycloaddition to the preparation of oxa-bridged carbocycles (Scheme 25). This transformation was proposed to proceed through a stepwise pathway. Attack of the olefin on the activated gold allylic carbocation generated from the allenamide should result in the formation of a carbocationic adduct (**25-I**). In the presence of the intramolecular ketone, this species may undergo nucleophilic attack by the neighboring carbonyl to form an oxocarbenium intermediate (**25-II**). A subsequent Prins-type reaction (nucleophilic addition of the vinyl–gold species onto this electrophilic moiety) and further elimination of gold(I) accounts for the formation of oxa-bridged polycycles.

The use of cationic gold(I) complexes was essential for this type of reactivity and their nature influenced significantly the stereochemical outcome of the reaction.[36] A highly electrophilic phosphite-bound gold catalyst provided the highest reactivity (0.5 mol % were sufficient to observe full conversion), and the *Z*/*E* selectivity of the *exo*-olefin was very high (22:1 *Z*/*E*). Several oxoalkenes were good reac-



Scheme 25. Proposed mechanism for the bicyclization of allenamides and oxoalkenes.

tion partners, reacting with terminal and internal allenamides and allenesufonamides to afford oxa-bridged cycloheptane derivatives in generally good yields and good to excellent diastereoselectivities when chiral oxoalkenes or allenamides were used. Remarkably, this cycloaddition was not only suited to the formation of 7-membered rings but also proved very efficient for the formation of oxa-bridged cyclooctanes and cyclononanes (Scheme 26). In addition, by use



Scheme 26. Gold(I)-catalyzed cycloaddition cascade of oxoalkenes and allenamides/allenesulfonamides.

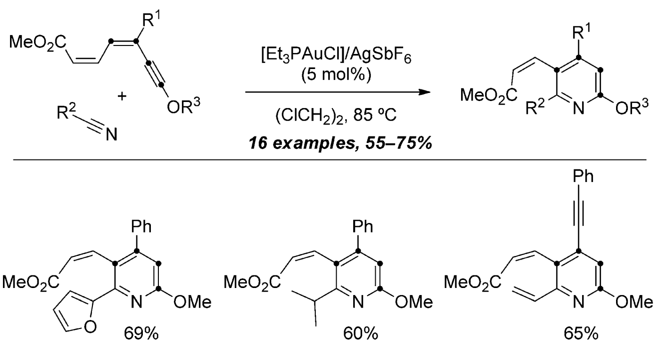
of chiral ligands, this transformation was further developed as an enantioselective process, with *ee* values ranging from 64–94 %.

3. Heterocycloadditions

A wide range of gold(I)-catalyzed heterocyclization reactions have been reported in the last years. Herein, we cover all the gold(I)-catalyzed intermolecular cycloaddition reactions in which the alkyne or allene partner does not undergo any rearrangement prior to the hetero-nucleophilic attack. Thus, reactions initiated by a gold(I)-promoted 1,2- or 1,3-acyloxy migration, which have been reviewed elsewhere,[37,38] are not covered. The diverse heterocycloadditions are classified based on mechanistic criteria.

3.1. Cycloadditions via trans-alkenylgold(I) intermediates

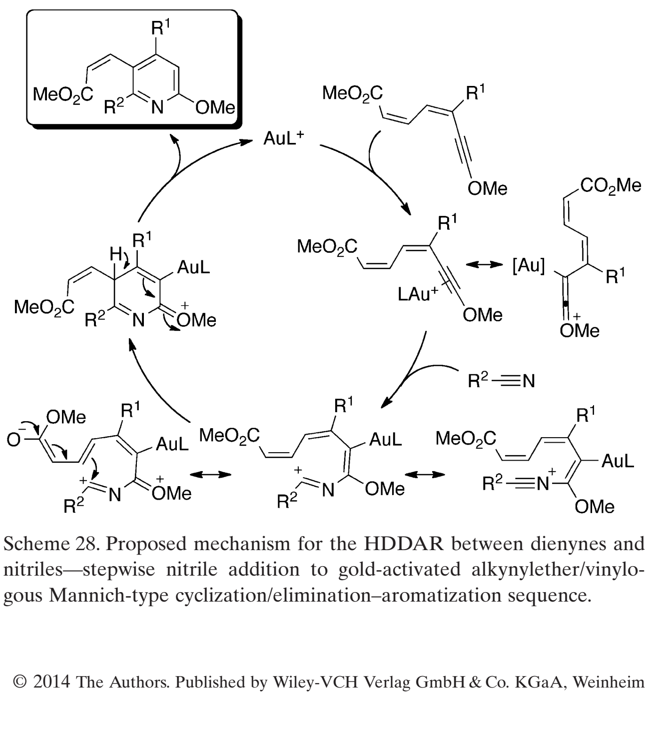
The first gold(I)-catalyzed HDDAR (hetero-dehydro-Diels–Alder reaction) was developed between dienynes and nitriles, which reacted smoothly in the presence of a gold(I) catalyst to yield pyridines (Scheme 27).[39] The formal [4+2]



Scheme 27. Gold(I)-catalyzed HDDAR between dienynes and nitriles.

reaction tolerated different substituents on the enyne partner. Furthermore, alkyl and (hetero)aromatic nitriles as well as vinyl nitrile could serve as nucleophilic partners.

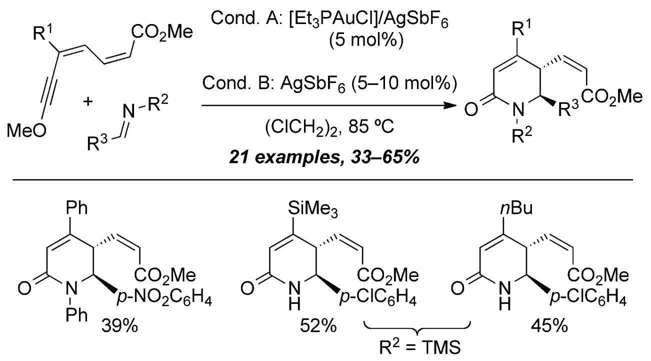
The proposed mechanism starts with the π-activation of 1,3-dien-5-ynes, followed by the nucleophilic attack of the nitrile (Scheme 28). The pyridines are formed stepwise by



Scheme 28. Proposed mechanism for the HDDAR between dienynes and nitriles—stepwise nitrile addition to gold-activated alkynylether/vinylogous Mannich-type cyclization/elimination–aromatization sequence.

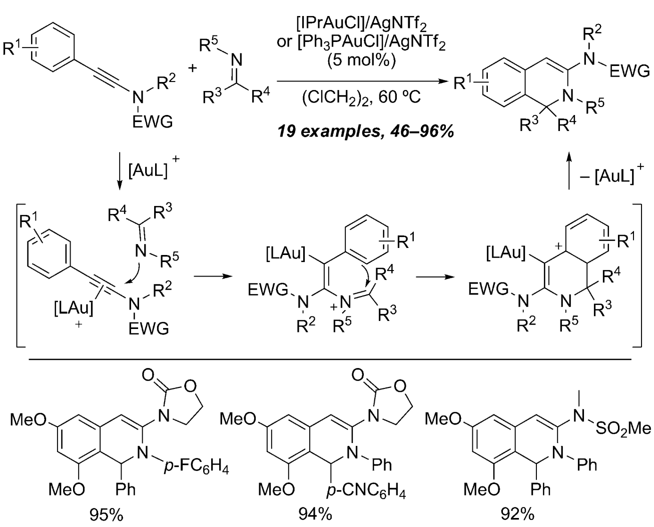
a Mannich-type cyclization, followed by an elimination–aromatization sequence.[39]

The main limitation of the reported methodology is the electronic requirement regarding the dienyne moiety: a push–pull system is needed. The reaction was later extended to the synthesis of 5,6-dihydropyridin-2-ones, by reacting the corresponding dienynes with aldimines or silylaldimines (Scheme 29).[40] In the latter case, the reaction can be catalyzed by simply using $AgSbF_6$. The cycloaddition takes place with complete diastereo- and regioselectivity.



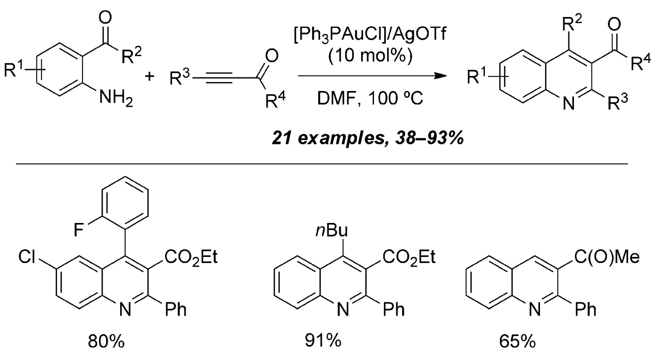
Scheme 29. Gold(I)-catalyzed HDDAR between dienynes and aldimines or silylaldimines.

Employing a somewhat similar strategy, a synthesis of dihydroisoquinolines (DHIQs) from imines and aryl yne-carbamates/yne-sulfonamides was developed. This formal [4+2] heterocycloaddition presumably proceeds via regioselective nucleophilic attack of the imine on the aryl-ynamine derivative and subsequent Pictet–Spengler-type cyclization of the arene onto the transient iminium moiety. As a consequence, only electron-rich aryl-substituted ynamine derivatives led to the efficient formation of DHIQs in moderate to excellent yields (Scheme 30).[41]



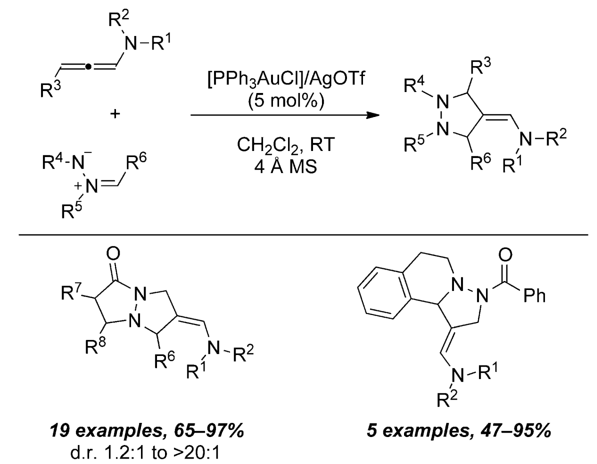
Scheme 30. Gold(I)-catalyzed formal [4+2] heterocycloaddition of arylynamine derivatives and imines for the preparation of DHIQs.

In order to prepare the parent quinolines, 2-aminoaryl carbonyls were treated with ketone-substituted internal alkynes in the presence of a catalytic amount of gold(I) complexes. This resulted in the formation of the desired polyfunctionalized heteroarenes in moderate to excellent yields (Scheme 31).[42] The reaction proceeded smoothly in DMF at 100 °C with $[Ph_3PAuCl]/AgOTf$ as a catalyst. Among the different aminoaryl coupling partners screened by varying the substituents at the aryl ring, electron-donating groups were found to give better results than strong electron-withdrawing substituents.



Scheme 31. Synthesis of polyfunctionalized quinolines through a gold(I)-catalyzed cycloaddition.

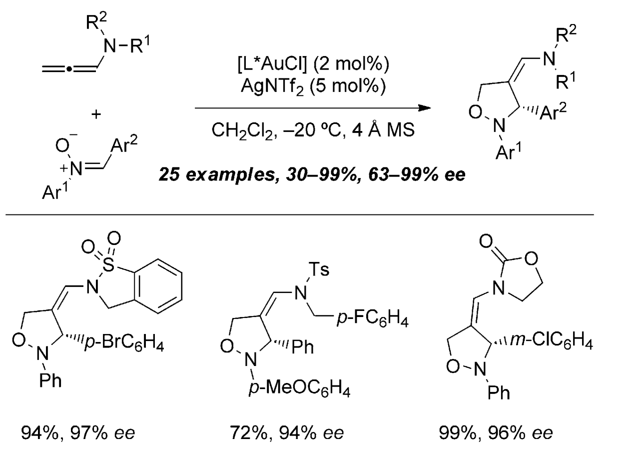
The dipolar [3+2]-cycloaddition of allenamides/sulfonamides and azomethine imines led to pyrazolidinone and dihydroisoquinoline cycloadducts in good to excellent yields employing $[PPh_3AuCl]/AgOTf$ (Scheme 32).[43] Although a thorough mechanistic study has not been performed, this cycloaddition presumably proceeds via nucleophilic attack of the azomethine imine on the activated gold allylic carbocation formed upon coordination of gold(I) to the allene derivative. Subsequent cyclization of the vinyl–gold moiety on



Scheme 32. Gold-catalyzed [3+2]-cycloaddition of azomethine imines and allenamides/sulfonamides.

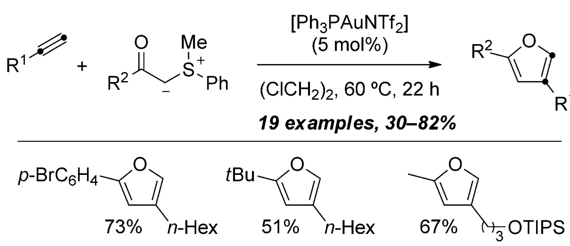
the iminium ion and protodeauration results in the formation of the observed cycloadducts.

Nitrones are also good dipoles in [3+2]-cycloadditions. The reaction of aryl-substituted nitrones with allenamides and allenesulfonamides under gold catalysis led to the formation of isoxazolidine derivatives (Scheme 33).[44] Moreover, through the use of chiral phosphoramidite ligands, this cycloaddition proved to be highly enantioselective, producing functionalized heterocycles usually with excellent enantiomeric excess (> 94 % *ee* in most cases).



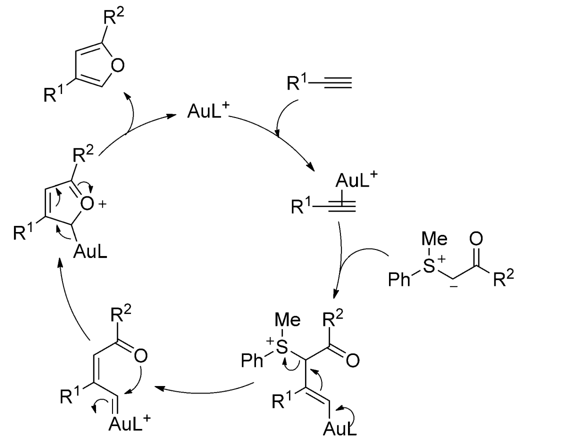
Scheme 33. Gold-catalyzed [3+2]-cycloaddition of nitrones and allenamides/sulfonamides.

With a fundamentally different approach, sulfur ylides were used as carbene transfer agents in the development of a synthesis for 2,4-disubstituted furans (Scheme 34).[45] The ylides reacted with terminal aliphatic alkynes in a [3+2]-cyclization fashion, using simple [PPh_3AuNTf_2] as a catalyst. The transformation tolerated silyl and alkyl ethers, sulfonamides, and carbamates on the alkyne partner as well as both electron-rich and -poor arylketo-ylides and aliphatic keto-ylides.



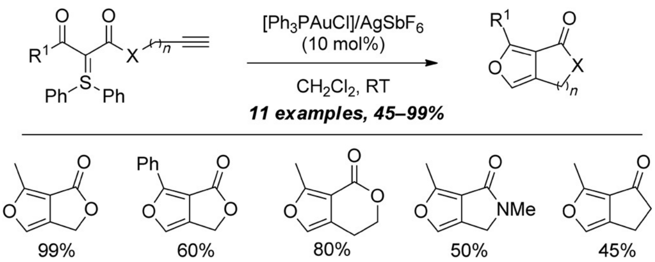
Scheme 34. Gold(I)-catalyzed [3+2] cyclization between terminal alkynes and sulfur ylides.

The reaction presumably starts with the regioselective attack at the (η^2-alkyne)gold(I) complex (Scheme 35).[45] Back donation of the gold center with concomitant expulsion of the leaving group generates an allylic gold–carbene that is trapped intramolecularly by the carbonyl group. A final demetalation generates the 2,4-disubstituted furans.

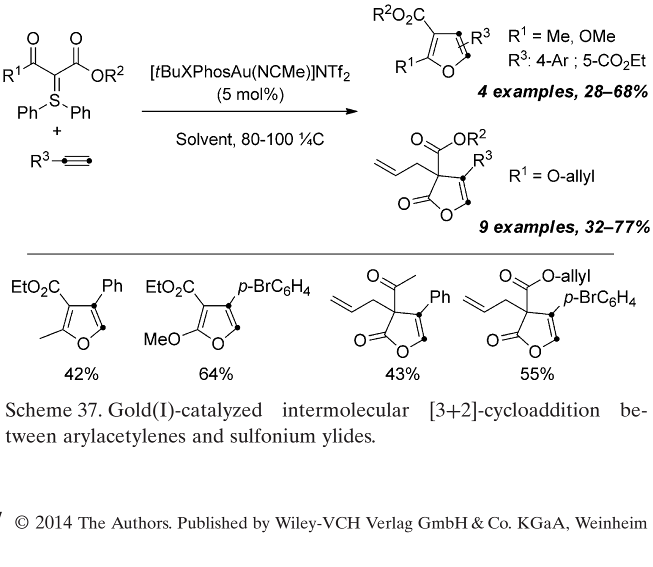


Scheme 35. Proposed mechanism of the gold(I)-catalyzed [3+2] cyclization between aliphatic alkynes and sulfur ylides—formation of gold–carbene/back donation of the gold center/intramolecular trapping by the carbonyl group.

A similar strategy involving carbene transfer to synthesize furans and furanones has recently been developed (Scheme 36 and 37).[46] Aryl acetylenes reacted with stabilized sulfonium ylides in the presence of gold(I) complexes bearing the bulky *t*BuXPhos ligand. The outcome of the reaction depended on the substituents on the sulfonium ylides. On one hand, when oxoester/oxoamide/1,3-diketone-derived



Scheme 36. Gold(I)-catalyzed intramolecular [3+2]-cycloaddition between arylacetylenes and sulfonium ylides.



Scheme 37. Gold(I)-catalyzed intermolecular [3+2]-cycloaddition between arylacetylenes and sulfonium ylides.

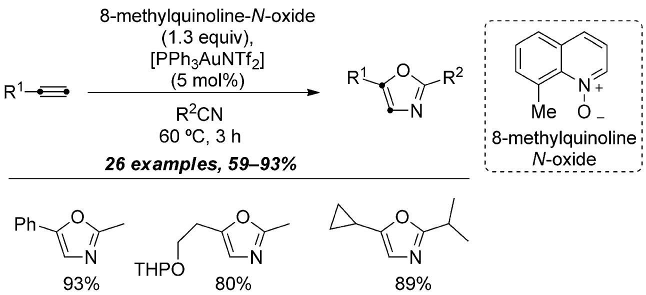
ylides were employed, furans were obtained with very high regioselectivity. In the intermolecular version of this reaction (Scheme 37), arylacetylenes were found to be the most suitable coupling partners, although furans could also be obtained in poor yields starting from alkyl propiolates. On the other hand, when diallylmalonate-derived ylides were used, furanones were formed instead.

The mechanism proposed for both reactions is analogous to the one suggested in Scheme 35.[45] In the case of the allyl substitution, once the furan is generated, a [3,3]-sigmatropic rearrangement of the allyl group takes place forming the quaternary center of the furanone.

3.2. α-Oxo/imido gold–carbene intermediates

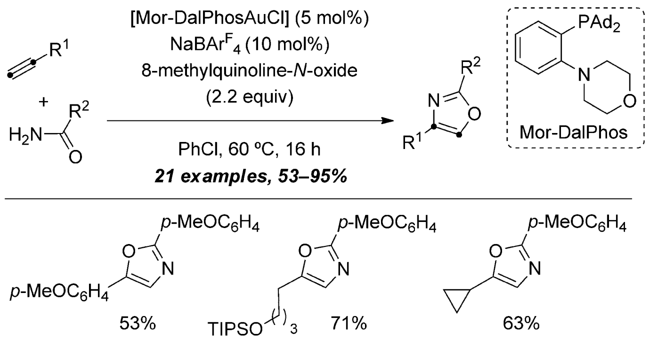
The oxidation of alkynes coordinated to gold(I) complexes using pyridine- or quinoline-*N*-oxide-type oxidants has been proposed to form highly electrophilic α-oxo gold(I)–carbenes.[47,48] The synthesis of α-functionalized ketones through this process circumvents the use of hazardous α-diazoketones. The resulting α-oxo gold–carbenes can be trapped intramolecularly by formal O–H,[47a,49] N–H,[50] and C–H[48b,51] insertions or by other nucleophilic partners.[52,53] However, it is important to note that in other related cases, the initial involvement of α-oxo gold(I)–carbene has been questioned.[54] So far, very little has been done regarding the intermolecular cycloaddition reactions of oxidized activated π-systems, mainly due to the high reactivity of the aforementioned intermediates.

The first gold(I)-catalyzed oxidative approach leading to a [2+2+1] annulation involved an alkyne, an external oxidant, and a nitrile source (Scheme 38).[53a] Thus, treating terminal alkynes bearing different substituents with aliphatic nitriles, benzonitriles, or phenylacetonitrile (used as solvents) in the presence of 8-methylquinoline-*N*-oxide and [$Ph_3PAuNTf_2$] resulted in the formation of 2,5-disubstituted oxazoles in good to excellent yields.



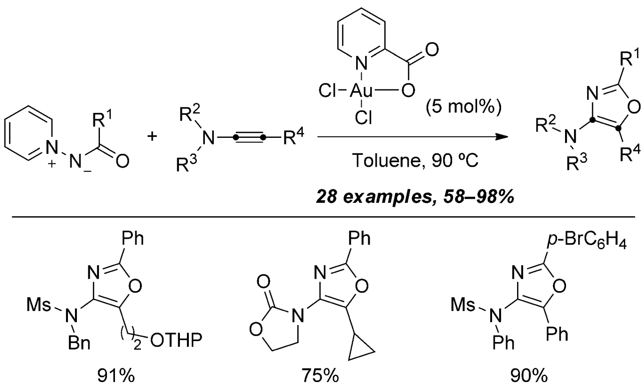
Scheme 38. Gold(I)-catalyzed oxidative [2+2+1] annulation of alkynes and nitriles in the presence of 8-methylquinoline-*N*-oxide.

The use of bulkier and bidentate ligands such as Mor-DalPhos allowed the trapping with an external nucleophile used in stoichiometric amount (Scheme 39).[53b] Terminal alkynes could be coupled to aromatic or α,β-unsaturated carboxamides through a [3+2] annulation using 8-methylquinoline-*N*-oxide and furnishing 2,4-disubstituted oxazoles. Three coordinated gold species were proposed as intermediates. They temper the reactivity of the α-gold–carbene by rendering it less electron-deficient, which leads to the observed chemoselective trapping. The non-phosphorous atom of the P,N- or P,S-bidentate ligands also coordinates to the gold atom, as supported by DFT calculations. Nucleophilic groups on the alkynyl moiety decreased the yield due to competition with the intramolecular trapping. A similar reaction with thioamides leads to 2,4-disubstituted thiazoles in good yields.[55]



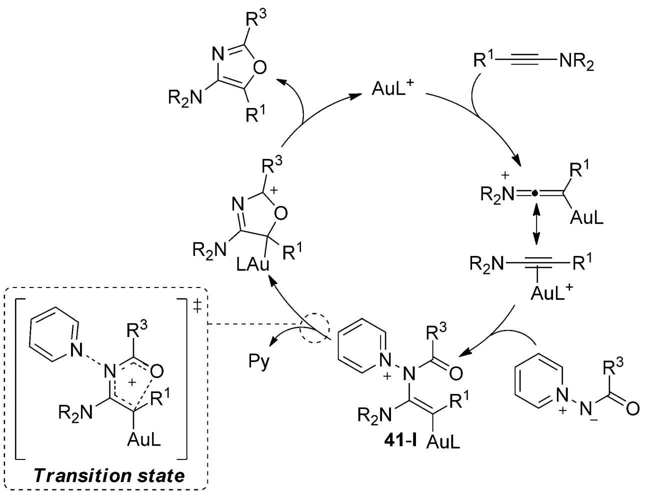
Scheme 39. Gold(I)-catalyzed oxidative [3+2] annulation between alkynes and carboxyamides.

Instead of using an oxygen-atom transfer agent (e.g., *N*-oxide), a nitrene transfer agent led to the synthesis of 2,4,5-trisubstituted oxazoles through a [3+2] cycloaddition reaction (Scheme 40).[56] In this case, the nucleophilic counterpart contained functionalities that formed the gold α-imidocarbenoid complex and could also close the ring though a 1,3-*N*,*O*-dipolar cycloaddition. The two-center reactants employed were pyridine-*N*-amidines that reacted with a wide range of functionalized ynamides or enol ethers. Although the optimized conditions required the use of dichloro(pyridine-2-carboxylato)gold(III) complex, the reaction also proceeds using gold(I) complexes.



Scheme 40. Gold(III)-catalyzed [3+2]-cycloaddition reaction between pyridine-*N*-amidines and ynamides or enol ethers.

The proposed mechanism starts with the coordination of the gold complex to the ynamide that undergoes a nucleophilic attack by the amidine adjacent to the ynamide nitrogen. The resulting cationic intermediate (**41**-**I**) cyclizes, forming the new C–O bond (Scheme 41).[56] Subsequent

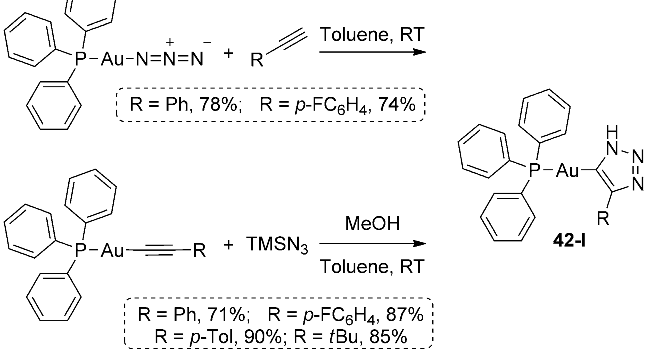


Scheme 41. Proposed mechanism for [3+2]-cycloaddition reaction between pyridine-*N*-amidines and ynamides or enol ethers.

elimination of the pyridine moiety through N–N bond cleavage and demetalation furnishes the oxazoles. More recently, the same procedure has been applied to non-symmetrical internal alkynes affording 2,4,5-(hetero)aryl-substituted oxazoles.[57]

3.3. Alkenylgold(I)–azide intermediates

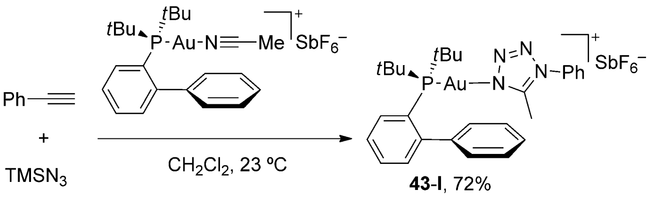
Since the first reported cycloaddition of (triphenylphosphine)gold(I)–azide to terminal alkynes, the use of azide as nucleophile has become more popular. Organogold products (**42**-**I**) could be isolated upon treatment of terminal alkynes with (triphenylphosphine)gold(I)–azide or by treating alkynyl gold(I) complexes with trimethylsilyl azide in protic solvents (Scheme 42).[58] The resulting organogold complexes



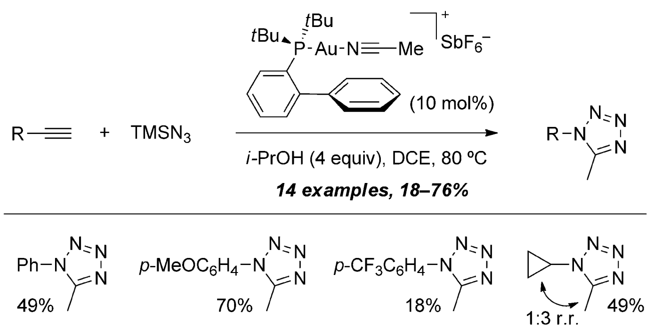
Scheme 42. Gold(I)-catalyzed [3+2]-cycloaddition of terminal alkynes and gold(I)-azide complexes and gold-acetylene complexes with $TMSN_3$.

were found to be stable, in contrast to their copper analogues.

Surprisingly, when the same reaction was carried out using [JohnPhosAu(NCMe)]SbF_6 instead, and CH_2Cl_2 as solvent, radically different products, such as tetrazole–gold(I) complex (**43**-**I**), were isolated (Scheme 43).[59]



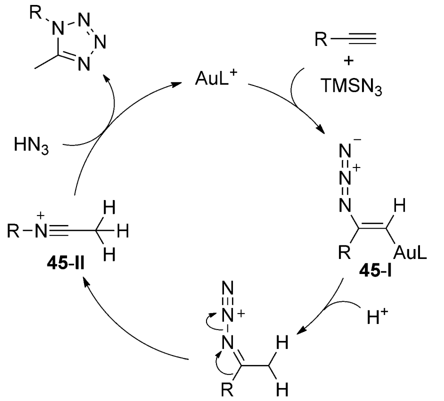
Scheme 43. Synthesis of tetrazole–gold(I) complex.



Scheme 44. Gold(I)-catalyzed synthesis of tetrazoles from alkynes through C–C bond cleavage.

This stoichiometric synthesis of gold(I)–tetrazole complexes was further developed into a catalytic procedure (Scheme 44).[59] Terminal alkynes were found to cyclize with $TMSN_3$ to give tetrazoles involving a C–C bond cleavage with concomitant insertion of four nitrogen atoms. The addition of *i*PrOH increased significantly the yield of the reaction. Aryl, heteroaryl, and alkyl groups were tolerated on the alkyne moiety, although for the latter, mixtures of regioisomers were obtained. Electron-withdrawing substituents on the aryl ring of the alkyne gave poor results; for instance, with 4-nitrophenylacetylene, no desired product was observed and 1-(1-azidovinyl)-4-nitrobenzene was isolated instead.

The mechanism proposed for the tetrazole synthesis starts with the attack of $TMSN_3$ on the π-activated triple bond, thus leading to the *trans* alkenylgold(I)–azide complex (**45**-**I**) (Scheme 45).[59,60] A Brønsted acid-catalyzed protodemetalation followed by migration of the R group forms the nitrilium cation (**45**-**II**). Competitive migration of the methyl group takes place if the substituent on the alkyne moiety is an alkyl chain. A final [3+2] cycloaddition reaction between HN_3 (formed by reaction of $TMSN_3$ with *i*PrOH) and (**45**-**II**) yields the tetrazoles. A similar mechanism has been proposed for the transformation of terminal alkynes into amides by use of $TMSN_3$ in the presence of [Ph_3PAuCl]/Ag_2CO_3 in aqueous TFA.[60]



Scheme 45. Proposed mechanism for the gold(I)-catalyzed synthesis of tetrazoles—formation of an alkenylgold(I)–azide species/R-migration through nitrogen loss/cycloaddition between nitrilium and azide.

It is worth noting that azide sources may react in a different manner with allenes; for instance, in this case, the gold catalyst activates the allenes towards nucleophilic azide addition and formation of allylic azides.[61]

3. Conclusion

The high selectivity of gold(I) towards alkynes (alkynophilicity) and, to a lesser extent, towards allenes, allows selective reactions of these substrates with differently substituted alkenes by processes in which the gold(I)-coordinated alkyne or allene acts as the electrophilic partner. In the case of monosubstituted alkynes, the competitive formation of non-reactive σ,π-digold complexes is an important side reaction that slows down the overall catalytic efficiency. Although several synthetically useful reactions have been developed, reactions of internal alkynes are still restricted to arylynamides or alkynyl ethers. Similarly, in the case of allenes, only substrates bearing electron-donating NR_2 or OR groups have been successful. Therefore, developing broadly applicable gold(I)-catalyzed cycloadditions of alkynes and allenes still remains a challenge.

Acknowledgements

We thank the European Research Council (Advanced Grant No. 321066), the MINECO (project CTQ2010-16088/BQU and FPI predoctoral fellowship to A.H.), the MECD (FPU predoctoral fellowship to C.O.), the AGAUR (2009 SGR 47), and the ICIQ Foundation for support of our work in this field.

[1] a) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; b) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; *Angew. Chem.* **2006**, *118*, 8064–8105; c) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; *Angew. Chem.* **2007**, *119*, 3478–3519; d) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; e) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; g) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; h) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; i) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; *Angew. Chem.* **2008**, *120*, 4338–4386; j) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; k) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954–1993; l) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; m) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912.
[2] a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406; *Angew. Chem.* **2004**, *116*, 2456–2460; b) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677–1693; c) C. Nieto-Oberhuber, S. López, E. Jiménez-Núñez, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 5916–5923; d) C. Ferrer, M. Raducan, C. Nevado, C. K. Claverie, A. M. Echavarren, *Tetrahedron* **2007**, *63*, 6306–6316; e) N. Cabello, C. Rodríguez, A. M. Echavarren, *Synlett* **2007**, 1753–1758; f) E. Jiménez-Núñez, C. K. Claverie, C. Bour, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895; *Angew. Chem.* **2008**, *120*, 8010–8013; g) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721–7730; h) V. López-Carrillo, N. Huguet, Á. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972–10978; i) P. Pérez-Galán, N. J. A. Martin, A. G. Campaña, D. J. Cárdenas, A. M. Echavarren, *Chem. Asian J.* **2011**, *6*, 482–486; j) A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.
[3] a) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 6350–6351; b) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun.* **2009**, 6451–6453.
[4] a) J. Urbano, A. J. Hormigo, P. de Frémont, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Chem. Commun.* **2008**, 759–761.
[5] P. N. Dickson, A. Wehrli, G. Geier, *Inorg. Chem.* **1988**, *27*, 2921–2925.
[6] C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16–28.
[7] V. López-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.
[8] a) A. Fürstner, C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307; b) M. Shi, L.-P. Liu, J. Tang, *J. Am. Chem. Soc.* **2006**, *128*, 7430–7431; c) A. Masarwa, A. Fürstner, I. Marek, *Chem. Commun.* **2009**, 5760–5763; d) T. William, J. Goodreid, N. Cockburn, *Curr. Org. Chem.* **2009**, *6*, 219–238.
[9] a) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179; b) E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5455–5459; *Angew. Chem.* **2006**, *118*, 5581–5585; c) P. Pérez-Galán, N. Delpont, E. Herrero-Gómez, F. Maseras, A. M. Echavarren, *Chem. Eur. J.* **2010**, *16*, 5324–5332.
[10] C. Obradors, D. Leboeuf, J. Aydin, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 1576–1579.
[11] Calculations performed with M06 6-31G* (C, H, P), LANL2DZ (Au) (Spartan 08) using PMe_3 as a model.
[12] a) S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 6029–6032; *Angew. Chem.* **2006**, *118*, 6175–6178; b) C. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952–11954.
[13] R. B. Dateer, B. S. Shaibu, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 113–117; *Angew. Chem.* **2012**, *124*, 117–121.
[14] H.-S. Yeom, J. Koo, H.-S. Park, Y. Wang, Y. Liang, Z.-X. Yu, S. Shin, *J. Am. Chem. Soc.* **2012**, *134*, 208–211.
[15] a) W. R. Dolbier, H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471–477; b) J. M. Um, H. Xu, K. N. Houk, W. Tang, *J. Am. Chem. Soc.* **2009**, *131*, 6664–6665; c) Y. Liang, L. Jiao, S. Zhang, Z.-X. Yu, J. Xu, *J. Am. Chem. Soc.* **2009**, *131*, 1542–1549.
[16] C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547–3551.

[17] E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327–7329.
[18] a) Q. Zhou, X. Chen, D. Ma, *Angew. Chem. Int. Ed.* **2010**, *49*, 3513–3516; *Angew. Chem.* **2010**, *122*, 3591–3594; b) K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517–3519; *Angew. Chem.* **2010**, *122*, 3595–3597.
[19] a) C. Wei, C. J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; b) V. Lavallo, G. D. Frey, S. Kousar, B. Donnadieu, G. Bertrand, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13569–13573; c) P. H. Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526; d) T. N. Hooper, M. Green, C. A. Russell, *Chem. Commun.* **2010**, *46*, 2313–2315; e) A. Simonneau, F. Jaroschik, D. Lesage, M. Karanik, R. Guillot, M. Malacria, J.-C. Tabet, J.-P. Goddard, L. Fensterbank, V. Gandon, Y. Gimbert, *Chem. Sci.* **2011**, *2*, 2417–2422; f) A. Grirrane, H. Garcia, A. Corma, E. Álvarez, *ACS Catal.* **2011**, *1*, 1647–1653; g) T. J. Brown, R. A. Widenhoefer, *Organometallics* **2011**, *30*, 6003–6009; h) M. Raducan, M. Moreno, C. Bour, A. M. Echavarren, *Chem. Commun.* **2012**, *48*, 52–54; i) A. S. K. Hashmi, T. Lauterbach, P. Nösel, M. H. Vilhelmsen, M. Rudolph, F. Rominger, *Chem. Eur. J.* **2013**, *19*, 1058–1065; j) A. Gómez-Suárez, S. Dupuis, A. M. Z. Slawin, S. P. Nolan, *Angew. Chem. Int. Ed.* **2013**, *52*, 938–942; *Angew. Chem.* **2013**, *125*, 972–976; k) A. Zhdanko, M. Ströbele, M. E. Maier, *Chem. Eur. J.* **2012**, *18*, 14732–14744; l) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 4456–4460; *Angew. Chem.* **2012**, *124*, 4532–4536; m) B. Rubial, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2013**, *355*, 3337–3343; n) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864–876.
[20] A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221–228.
[21] N. Huguet, D. Leboeuf, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 6581–6585.
[22] a) A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713; b) For the first report of a gold-catalyzed formation of phenols from furan-ynes, see: A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
[23] For a mechanistic study on the related intramolecular formation of phenols from furan-ynes, see: A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats, W. Frey, *Chem. Eur. J.* **2008**, *14*, 3703–3708.
[24] Selected examples: a) P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349; b) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030.
[25] Selected examples: a) M. R. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403; b) H. Teller, S. Flügge, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2010**, *49*, 1949–1953; *Angew. Chem.* **2010**, *122*, 1993–1997.
[26] H. Faustino, F. López, L. Castedo, J. L. Mascareñas, *Chem. Sci.* **2011**, *2*, 633–637.
[27] G. Wang, Y. Zou, Z. Li, Q. Wang, A. Goeke, *Adv. Synth. Catal.* **2011**, *353*, 550–556.
[28] a) L.-L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773–782; b) A. W. Hill, M. R. J. Elsegood, M. C. Kimber, *J. Org. Chem.* **2010**, *75*, 5406–5409; c) M. C. Kimber, *Org. Lett.* **2010**, *12*, 1128–1131.
[29] J. Francos, F. Grande-Carmona, H. Faustino, J. Iglesias-Sigüenza, E. Díez, I. Alonso, R. Fernández, J. M. Lassaletta, F. López, J. L. Mascareñas, *J. Am. Chem. Soc.* **2012**, *134*, 14322–14325.
[30] S. Montserrat, H. Faustino, A. Lledós, J. L. Mascareñas, F. López, G. Ujaque, *Chem. Eur. J.* **2013**, *19*, 15248–15260.
[31] V. Pirovano, L. Decataldo, E. Rossi, R. Vicente, *Chem. Commun.* **2013**, *49*, 3594–3596.
[32] H. Faustino, P. Bernal, L. Castedo, F. López, J. L. Mascareñas, *Adv. Synth. Catal.* **2012**, *354*, 1658–1664.
[33] S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555; *Angew. Chem.* **2012**, *124*, 11720–11723.
[34] S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J. M. González, *Adv. Synth. Catal.* **2012**, *354*, 1651–1657.
[35] X.-X. Li, L.-L. Zhu, W. Zhou, Z. Chen, *Org. Lett.* **2012**, *14*, 436–439; Corrigemdum: X.-X. Li, L.-L. Zhu, W. Zhou, Z. Chen, *Org. Lett.* **2012**, *14*, 1185.
[36] H. Faustino, I. Alonso, J. L. Mascareñas, *Angew. Chem. Int. Ed.* **2013**, *52*, 6526–6530; *Angew. Chem.* **2013**, *125*, 6654–6658.
[37] a) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692–706; b) X.-Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698–7711.
[38] a) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750–2752; *Angew. Chem.* **2007**, *119*, 2806–2809; b) J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350–1357; c) E. Soriano, J. Marco-Contelles, *Chem. Eur. J.* **2008**, *14*, 6771–6779; d) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem. Int. Ed.* **2008**, *47*, 718–721; *Angew. Chem.* **2008**, *120*, 730–733; e) Y. Zou, D. Garayalde, Q. Wang, C. Nevado, A. Goeke, *Angew. Chem. Int. Ed.* **2008**, *47*, 10110–10113; *Angew. Chem.* **2008**, *120*, 10264–10267; f) N. Marion, G. Lemière, A. Correa, C. Costabile, R. S. Ramón, X. Moreau, P. de Frémont, R. Dahmane, A. Hours, D. Lesage, J.-C. Tabet, J.-P. Goddard, V. Gandon, L. Cavallo, L. Fensterbank, M. Malacria, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 3243–3260; g) C. Fehr, B. Winter, I. Magpantay, *Chem. Eur. J.* **2009**, *15*, 9773–9784; h) P. Mauleón, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 4513–4520; i) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462–1479.
[39] J. Barluenga, M. Á. Fernández-Rodríguez, P. García-García, E. Aguilar, *J. Am. Chem. Soc.* **2008**, *130*, 2764–2765.
[40] J. M. Fernández-García, M. Á. Fernández-Rodríguez, P. García-García, E. Aguilar, *Org. Lett.* **2011**, *13*, 5172–5175.
[41] Z. Xin, S. Kramer, J. Overgaard, T. Skrydstrup, *Chem. Eur. J.* **2014**, DOI: 10.1002/chem.201403290.
[42] S. Cai, J. Zeng, Y. Bai, X.-W. Liu, *J. Org. Chem.* **2012**, *77*, 801–807.
[43] W. Zhou, X.-X. Li, G.-H. Li, Y. Wu, Z. Chen, *Chem. Commun.* **2013**, *49*, 3552–3554.
[44] G.-H. Li, W. Zhou, X.-X. Li, Q.-W. Bi, Z. Wang, Z.-G. Zhao, W.-X. Hu, Z. Chen, *Chem. Commun.* **2013**, *49*, 4770–4772.
[45] S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2012**, *51*, 4681–4684; *Angew. Chem.* **2012**, *124*, 4759–4762.
[46] X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 8886–8890; *Angew. Chem.* **2012**, *124*, 9016–9020.
[47] a) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259; b) W. He, L. Xie, Y. Xu, J. Xiang, L. Zhang, *Org. Biomol. Chem.* **2012**, *10*, 3168–3171; c) K. Ji, Y. Zhao, L. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6508–6512; *Angew. Chem.* **2013**, *125*, 6636–6640.
[48] a) S. Ghorpade, M.-D. Su, R.-S. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 4229–4234; *Angew. Chem.* **2013**, *125*, 4323–4328; b) G. Henrion, T. E. J. Chavas, X. Le Goff, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6277–6282; *Angew. Chem.* **2013**, *125*, 6397–6402.
[49] L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.
[50] L. Ye, W. He, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3236–3239; *Angew. Chem.* **2011**, *123*, 3294–3297.
[51] a) B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 14070–14072; b) L.-Q. Yang, K.-B. Wang, C.-Y. Li, *Eur. J. Org. Chem.* **2013**, 2775–2779.
[52] a) P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2011**, *47*, 379–381; b) C.-F. Xu, M. Xu, Y.-X. Jia, C.-Y. Li, *Org. Lett.* **2011**, *13*, 1556–1559.
[53] a) W. He, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485; b) Y. Luo, K. Ji, Y. Li, L. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 17412–17415.
[54] a) L. Cui, Y. Peng, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395; b) L. Cui, L. Ye, L. Zhang, *Chem. Commun.* **2010**, *46*, 3351–3353; c) E. L. Noey, Y. Luo, L. Zhang, K. N. Houk, *J. Am. Chem. Soc.* **2012**, *134*, 1078–1084.
[55] G. Wu, R. Zheng, J. Nelson, L. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1229–1234.

[56] P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935; *Angew. Chem.* **2011**, *123*, 9093–9097.
[57] E. Chatzopoulou, P. W. Davies, *Chem. Commun.* **2013**, *49*, 8617–8619.
[58] D. V. Partyka, J. B. Updegraff III., M. Zeller, A. D. Hunter, T. G. Gray, *Organometallics* **2007**, *26*, 183–186.
[59] M. Gaydou, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 13468–13471; *Angew. Chem.* **2013**, *125*, 13710–13713.
[60] C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 7850–7854; *Angew. Chem.* **2013**, *125*, 8004–8008.
[61] C. Hurtado-Rodrigo, S. Hoehne, M. P. Muñoz, *Chem. Commun.* **2014**, *50*, 1494–1496.

Received: April 16, 2014
Published online: July 22, 2014

