Optimising Catalyst and Reaction Conditions in Gold Catalysis – Ligand Development

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Abstract

This review considers phosphine and *N*-heterocyclic carbene complexes of gold(I) that are used as (pre-)catalysts for a range of reactions in organic synthesis. These are divided according to the structure of the ligand, with the narrative focussing on studies that offer a quantitative comparison between the ligands and readily available or widely used existing systems.

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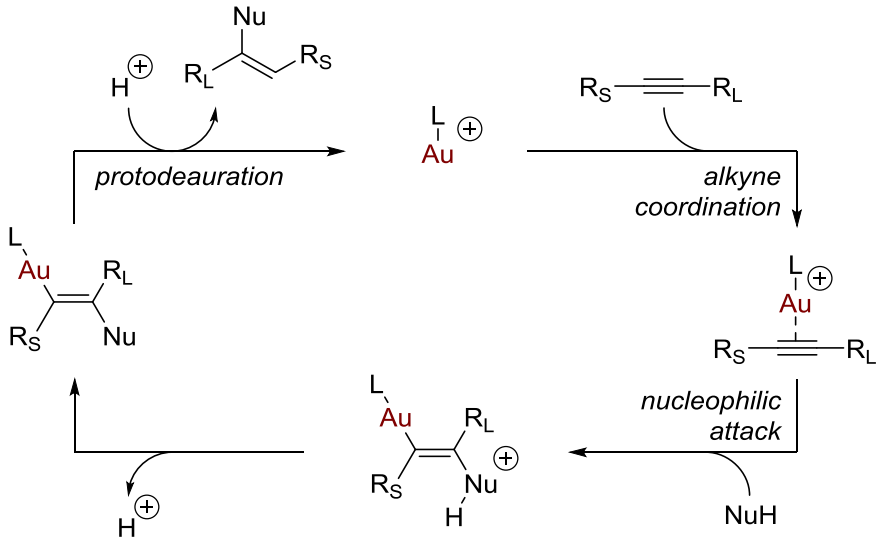
Contents

1 Introduction

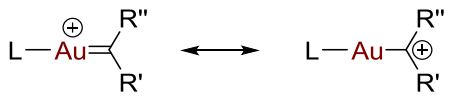
1.1 Basic Principles of Gold Catalysis

The properties and reactivity of gold are heavily influenced by relativistic effects, including the colour of the metal itself.[1] Gold tends to form rather strong bonds to ligands and is often reluctant to undergo oxidation state changes, which means that gold-catalysed reactions can often be carried out under air. Cationic gold(I) complexes, which are the active catalyst in most gold-catalysed reactions, readily coordinate alkenes, allenes, and alkynes,[2] and activate these towards nucleophilic attack. Gold very rarely undergoes β-hydride elimination, and instead can be readily replaced by a proton during the process of protodeauration. This has allowed a wide range of intra- and intermolecular alkene, allene, and alkyne functionalisation reactions to be developed, for which a very general catalytic cycle (using alkynes as an example) is provided in Scheme 1. In addition, gold can stabilise adjacent carbenium ions – often represented as gold carbenes[3] – and therefore allow reactions such as the oxidative difunctionalisation of unsaturated carbon-carbon bonds and the formation of cyclopropanes and cyclobutanes, either as the ultimate product or en route to other products as part of skeletal rearrangement cascades (Scheme 2). The synthetic capabilities of gold catalysis have been extensively reviewed.[4-8]

Scheme 1. A general catalytic cycle for gold-catalysed alkyne functionalisation.



Scheme 2. Two representations of gold carbene species.



1.2 Key Steps and Rate-Determining Steps in Gold Catalysis

The majority of studies in gold catalysis measure the outcome of a series of reactions in terms of conversion to product – assessed using, for example, GC-FID analysis or NMR spectroscopy – or in terms of isolated yield. While these measures tell us how useful a given reaction is overall, it provides limited insight into what is actually going on in the various steps of the reaction. Some researchers have attempted to use kinetic studies to provide a broad comparison of different ligands, and these are discussed towards the end of this review. However, in order to frame some of the subsequent discussion, it is worth briefly noting the outcomes from the study conducted by Wang *et al.* in which ligand effects on a series of different reactions were considered.[9] Each reaction was considered to be rate-limited by a different step or process, either: electronic activation of the alkene, allene, or alkyne; protodeauration; electronic activation, amid significant catalyst deactivation; or protodeauration amidst significant catalyst deactivation. The requirements for a 'good' ligand depend on this classification:

- **Rate-limiting electronic activation**: In these scenarios, the rate-determining step is the reaction of the nucleophile with a gold-alkene/alkyne/allene complex. It is anticipated that the formation of the gold-alkene/alkyne/allene complex is unlikely to be rate-determining itself, because the alkene/alkyne/allene is typically the best ligand for the L-Au^+ complex by a significant margin. This mechanistic scenario is typically encountered with weak nucleophiles or less reactive substrates such as alkenes and allenes. An *electron-poor* ligand should perform best.
- **Rate-limiting protodeauration**: This can be encountered where the nucleophilic attack step is fast and/or the reaction is intramolecular. An *electron-rich* ligand should perform best.
- **Rate-limiting electronic activation; significant catalyst deactivation:** Reactions with weak nucleophiles and less reactive unsaturated carbon-carbon linkages may suffer from rapid catalyst deactivation. This can be mitigated using bulkier, less electron-rich ligands, such as (*o*-biaryl)di(aryl)phosphines.
- **Rate-limiting protodeauration; significant catalyst deactivation:** Reactions with basic nucleophiles such as alkylamines can lead to slow protodeauration due to the neutralisation of acid in the reaction mixture. If catalyst deactivation is then significant, overall conversion is limited. The best ligands for these types of reactions are often bulky, electron-rich ligands, such as "Buchwald-type" (*o*-biaryl)di(alkyl)phosphine ligands, where the alkyl group is typically *tert*-butyl, cyclohexyl, or adamantly or the larger members of the NHC family, such as IPr.

This necessarily reflects a somewhat simplistic view of gold catalysis, but provides a reasonable initial approach to considering the interplay between ligand properties and the reaction mechanism, at least before any detailed study of a specific reaction under specific conditions is carried out.

1.3 Ligands and Ligand Properties

The most commonly employed ancillary ligands in gold catalysis are phosphines and *N*-heterocyclic carbene (NHC) ligands. The stereoelectronic properties of these ligands can be easily tuned by chemical modification, and these properties have a great impact on the [Au-L] catalytic activity.[10,11] Many efforts have been devoted to the characterisation of the steric and electronic properties of ancillary ligands in order to better understand the ligand influence and to design new catalytic systems, and various descriptors have been established.[12-18]

Both families of complexes form strong Au-L bonds, with NHCs being more electron-donating than phosphines (with some exceptions). Phosphines are σ-donor/π-acceptor ligand; NHCs, which were initially considered as pure σ-donor ligands, are also π-accepting and π-donating ligands. In both cases, the extent of the π- contributions depend on the ligand structure and the nature of the metal center.[15,19] The overall donating ability is typically characterised using the Tolman Electronic Parameter (TEP), based on the CO IR stretching frequencies of M-L-carbonyl species.[12,20-24] The σ-donating component has been quantified with the Huynh Electronic Parameter (HEP), which can be obtained by recording the ^{13}C NMR spectra of Pd(II)-NHC species.[13,25,26]

In the case of NHCs, the π-accepting contribution can be spectroscopically obtained by measuring the ^{31}P or ^{77}Se NMR spectrum of the corresponding NHC-phosphinidene[27] and NHC-selenourea[28] complexes, respectively. These methodologies have been applied to a large range of NHCs.[29] Other methods include the measurement of $^{1}J_{Pt\text{-}C}$ NMR coupling constants in $[PtCl_2(DMSO)(NHC)]$ species[20] or the calculated CO IR stretching frequency of $[Au(NHC)(CO)]^+$ complexes.[22] Additionally, DFT calculations can be employed to calculate the HOMO and LUMO energies of the carbenes as a measure of their σ-donor and π-acceptor properties, respectively. A comprehensive review of NHC electronic descriptors has recently been reported.[13]

The classical parameter to characterise the steric volume of phosphorous ligands is the Tolman Cone Angle.[11] This descriptor is not useful for NHC ligands, due to their different shape, and the percent buried volume (%V_{bur}), which can also be used for phosphines as well, is used instead.[30,31] This parameter represents the percentage of a theoretical sphere around the metal centre that is occupied by the ligand[30] and can be calculated using the Samb*V*ca software.[32,33] This software also allows for the calculation of steric maps, showing the steric impacts of the ligands per-quadrant.[33] It should be noted that the calculated %V_{bur} depends on the parameters employed in the calculation and

comparisons should be drawn from $\%V_{bur}$ obtained using the same parameters.[30] The steric and electronic properties of phosphine and NHC ligands are often invoked to explain M-L catalytic outcomes. Whenever available, these stereoelectronic descriptors will be discussed.

1.4 Scope of this Review

This review covers the literature up until mid-2020 and focusses on the systematic study of how ancillary phosphine and NHC ligand structure can affect the outcomes of catalysis by homogeneous gold(I) complexes; the chemistry of gold(III) and its relevance to catalysis are discussed in depth elsewhere.[34] The focus here is on phosphorus and NHC ligands because these are the most widely used ligands for catalysis by homogeneous gold(I) complexes.

Enantioselective gold catalysis is omitted from this review, because this necessarily completely changes the approach to ligand design, and because this area has been reviewed recently.[4,35] This review does not consider heterogeneous or supported or immobilised gold catalysts, gold cluster chemistry, heterobimetallic complexes that include gold centres, the photophysical applications of gold complexes, the use of gold complexes as diagnostic or therapeutic agents, or supramolecular assemblies incorporating gold complexes; these applications will all require different approaches to ligand design. We also exclude reactions that are catalysed by multiple metals or via metal/gold dual catalysis,[36] photoredox/gold catalysis,[37,38] organo/gold dual catalysis, or electrochemical gold catalysis;[39] we refer interested readers to relevant reviews on these topics where these are available.

It is important to note that rigorously and fairly comparing ligands can be very challenging. In surveying the literature, it is apparent that the choice of benchmark reaction, or the conditions under which it is performed, can vary considerably between manuscripts, and in many cases even within a single manuscript. Single point yield or conversion measurements often do not tell the whole story, and the degree of error in the measurement of yield or conversion is often not explored. In order to achieve the fairest and most robust comparisons between ligand systems we have focussed on reactions that proceed with <5 mol% of a gold catalyst, and only report studies where new ligands are benchmarked against a common or readily-available ligand to allow the results to be considered in context.

2 Phosphorus Ligands

Phosphine ligands are amongst the most commonly employed ligands for homogeneous catalysis with gold; these are frequently paired with gold(I) complexes. In addition to phosphines, a number of other phosphorus donors have been trialled as ligands for homogeneous gold catalysis. While simple phosphine ligands such as trimethylphosphine and triphenylphosphine can enable a wide range of catalysis and synthetic chemistry, researchers have explored a very wide area of chemical space in the search for more effective ligands and to design catalysts for specific reactions or reaction conditions. The ligands considered in this section are displayed in Figure 1. Note that where a ligand has a commonly-used trivial name or short chemical formula this will be used interchangeably with the compound number.

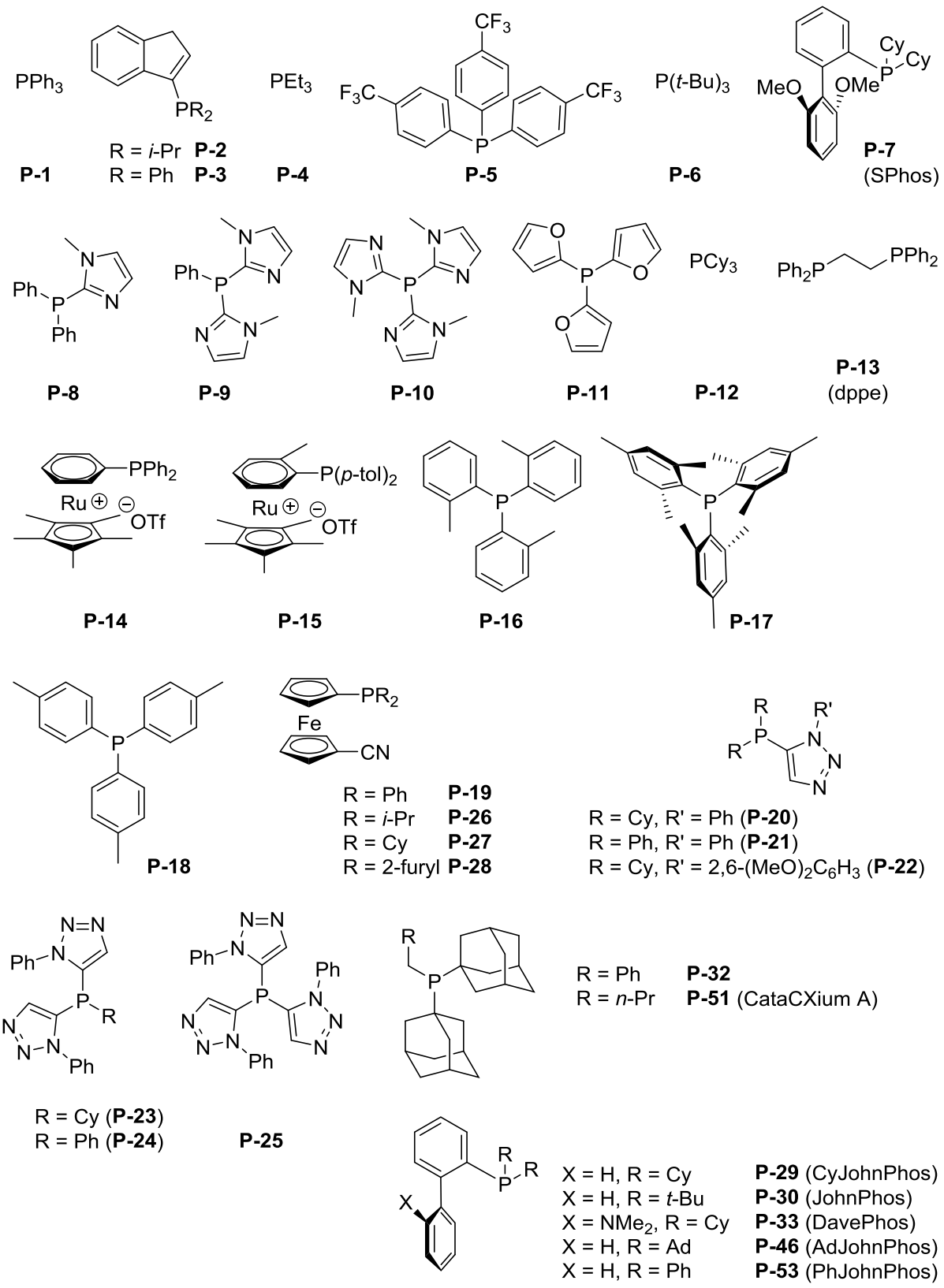
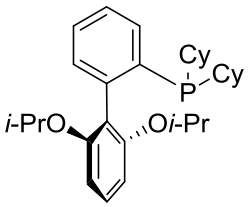
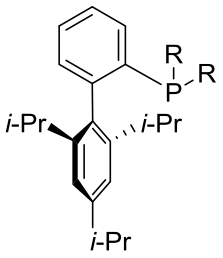


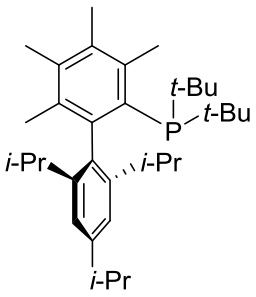
Figure 1. Phosphorus ligands considered in this review.



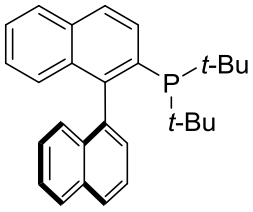
P-34 (RuPhos)



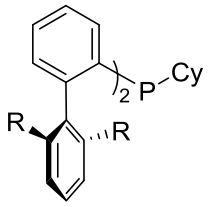
R = Cy **P-31** (XPhos)
R = *t*-Bu **P-36** (*t*-BuXPhos)
R = (3,5-$(F_3C)_2C_6H_3$) **P-38** (3,5-$(F_3C)_2C_6H_3$)XPhos
R = Ph **P-42** (PhXPhos)



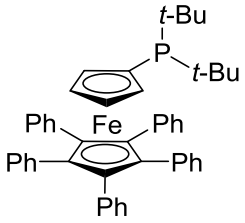
P-35 (Me_4*t*-BuXPhos)



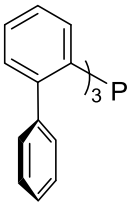
P-37 (TrixiePhos)



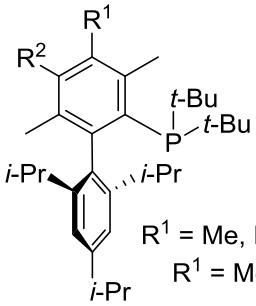
R = O*i*-Pr **P-39** (BiPhePhos)
R = H **P-44**



P-40 (QPhos)

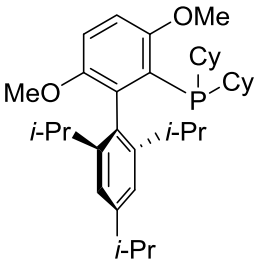


P-41

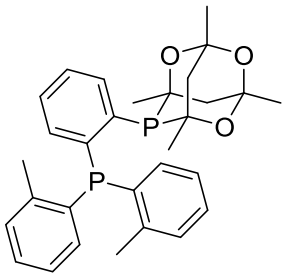


R^1 = Me, R^2 = MeO *or*
R^1 = MeO, R^2 = Me

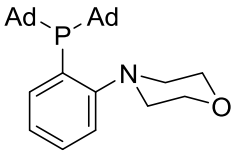
P-43 (Me_3(MeO)XPhos)



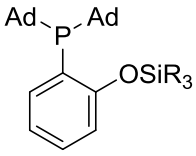
P-45 (BrettPhos)



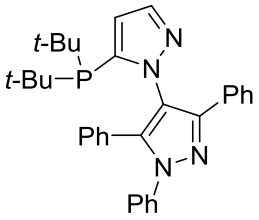
P-47 (PAd-DalPhos)



P-48 (Mor-DalPhos)



R = *i*-Pr **P-49** (OTIPSDalPhos)
R = *t*-Bu **P-52** ((*t*-Bu_3SiO)DalPhos)



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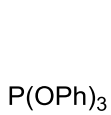

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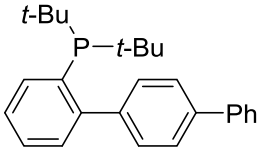

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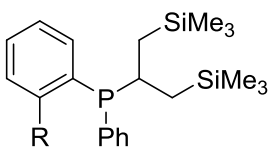
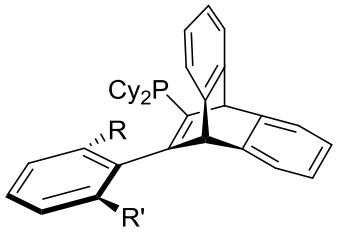
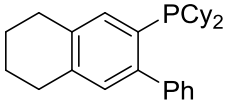


R = $CHPh_2$ **P-56**
R = Ph **P-57**
R = CH_2CH_2Ph **P-58**

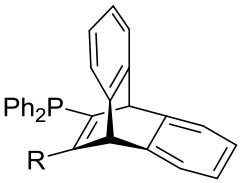
Figure 1 (continued). Phosphorus ligands considered in this review.



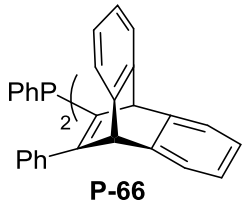
R = R' = H **P-59**
R = H, R' = OMe **P-60**
R = R' = Me **P-61**
R = R' = OMe **P-62**



P-63



R = H **P-64**
R = Ph **P-65**



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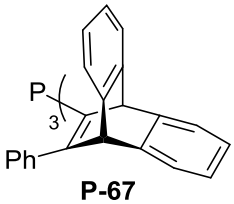

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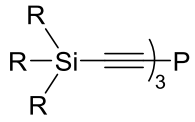
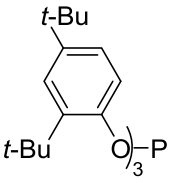


R = 3,5-(*t*-Bu)$_2$-4-(MeO)C$_6$H$_2$ **P-68**
R = 3,5-(Me$_3$Si)C$_6$H$_3$ **P-69**
R = Ph **P-70**
R = *i*-Pr **P-71**



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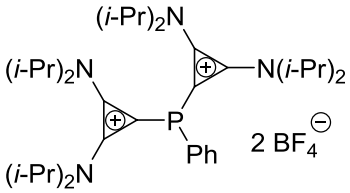

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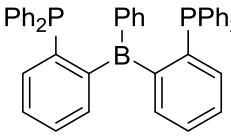

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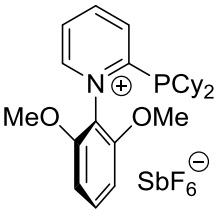

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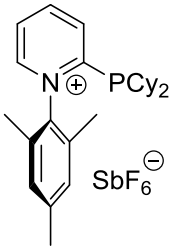

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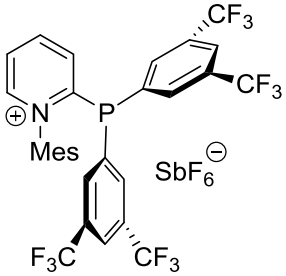

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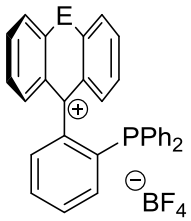
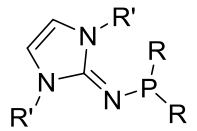
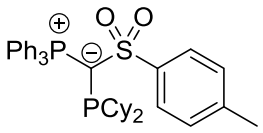


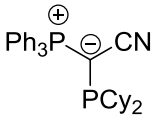
E = NH **P-78**
E = O **P-79**



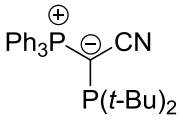
R = *t*-Bu R' = Mes **P-80**
R = *t*-Bu R' = 2,6-(*i*-Pr)$_2$C$_6$H$_3$ **P-81**
R = *i*-Pr R' = Mes **P-82**
R = *i*-Pr R' = 2,6-(*i*-Pr)$_2$C$_6$H$_3$ **P-83**
R = *i*-Pr R' = *i*-Pr **P-84**



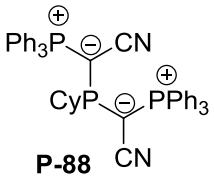
P-85



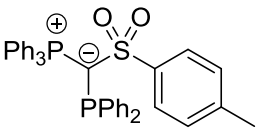
P-86



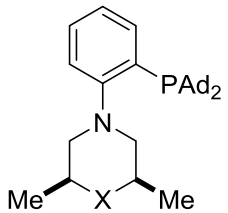
P-87



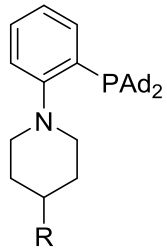
P-88



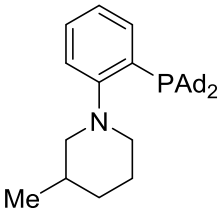
P-89



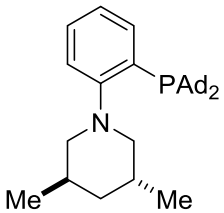
X = CH_2, R = Me **P-90**
X = O, R = Me **P-96**
X = O, R = Ph **P-97**



R = H **P-91**
R = Me **P-92**
R = *t*-Bu **P-93**



P-94



P-95

Figure 1 (continued). Phosphorus ligands considered in this review.

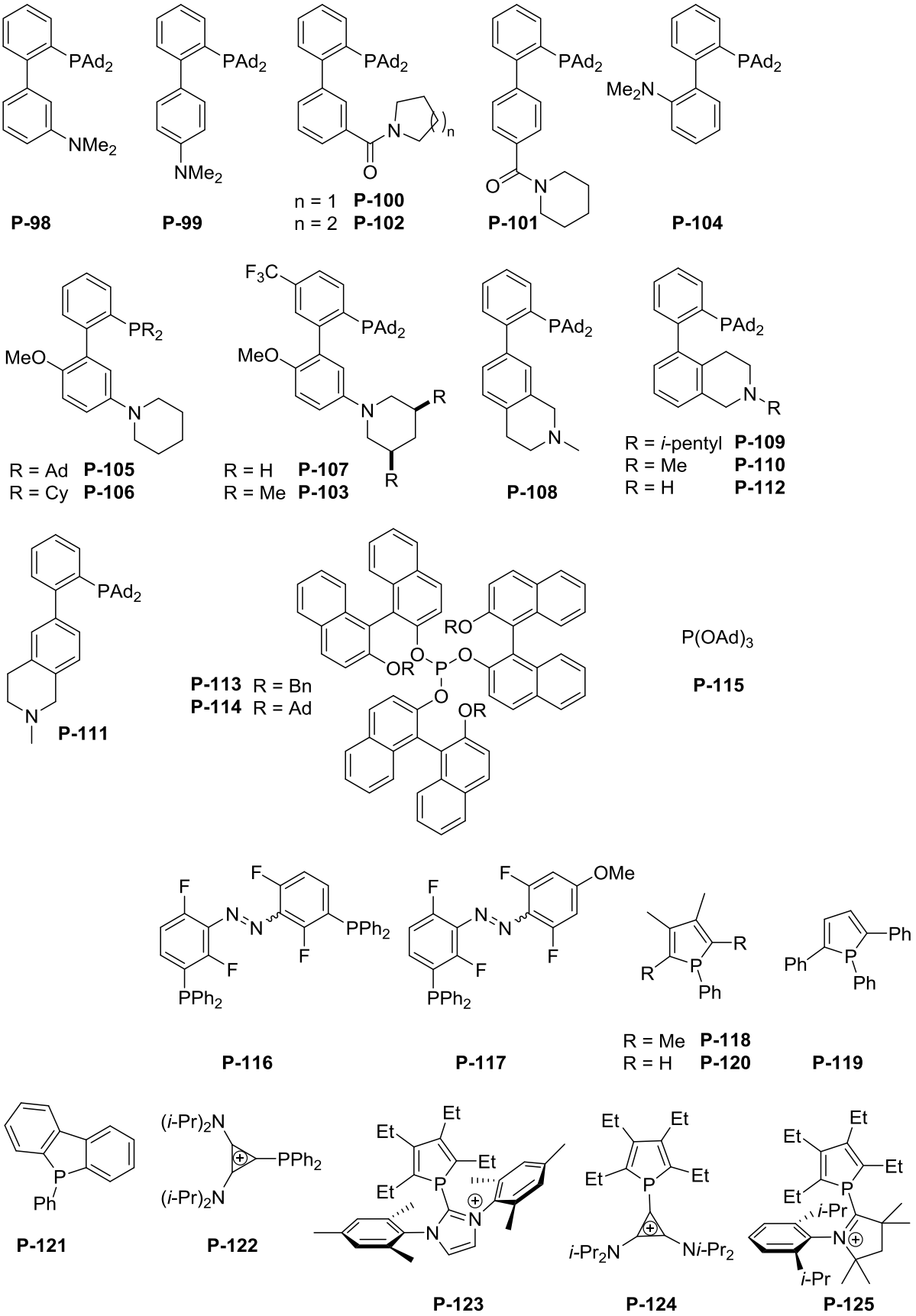


Figure 1 (continued). Phosphorus ligands considered in this review.

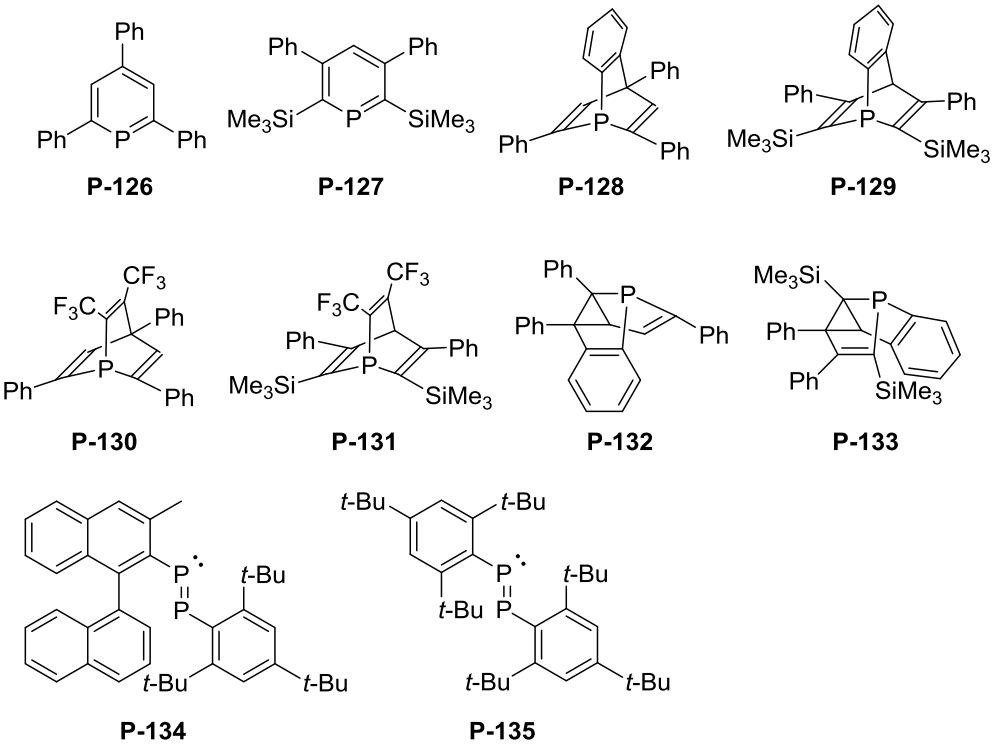


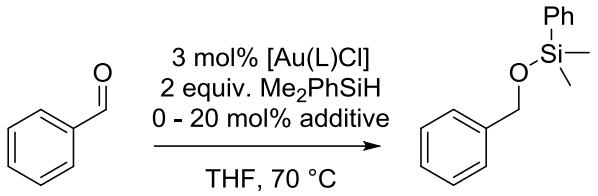
Figure 1 (continued). Phosphorus ligands considered in this review.

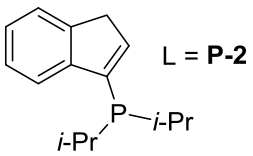
2.1 Phosphines with Simple Alkyl and/or Aryl Substituents

Triphenylphosphine is arguably the benchmark ligand in many respects, due to its ubiquity in homogenous catalysis, low cost, and bench stability. However, the steric and electronic properties of phosphines are readily tuned, and so researchers have explored a variety of such ligands.

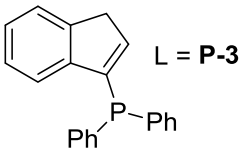
Wile *et al.* tested indenyldi(*iso*-propyl)phosphine (**P-2**) and indenyl(diphenyl)phosphine (**P-3**) in the gold-catalysed hydrosilylation of aldehydes (Scheme 3).[40] However, extensive screening of different ligands and aldehydes established that electron donating trialkylphosphines were optimal for this transformation, with the combination of P(*n*-Bu)$_3$ and [AuCl(SMe$_2$)] giving almost quantitative conversion after three hours.

Scheme 3. Gold-catalysed aldehyde hydrosilylation. Conversions were obtained by GC analysis.

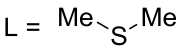




no additive	50% (24 h)
20 mol% **P-2**	99% (12 h)



no additive	47% (24 h)
20 mol% **P-3**	4% (24 h)

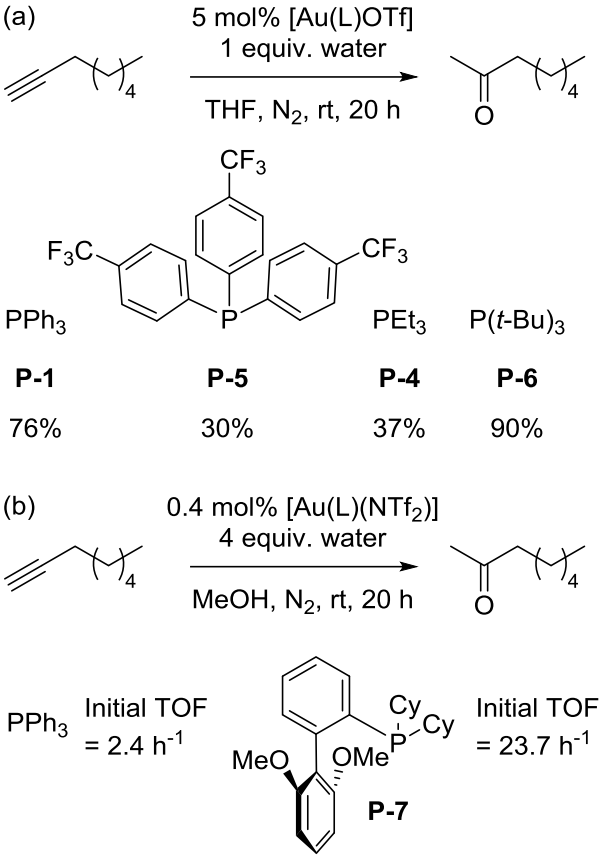


no additive	27% (3 h)
20 mol% PPh_3	2% (3 h)
20 mol% P(*n*-Bu)$_3$	98% (3 h)

Leyva and Corma have systematically compared some monodentate phosphines for the gold-catalysed hydration of alkynes, using 1-octyne as a model substrate (Scheme 4).[41] Electron-rich triethylphosphine (**P-4**) and electron-poor tris(*para*-trifluoromethylphenyl)phosphine (**P-5**) performed poorly, while decent results were obtained with triphenylphosphine and tri(*tert*-butyl)phosphine (**P-**

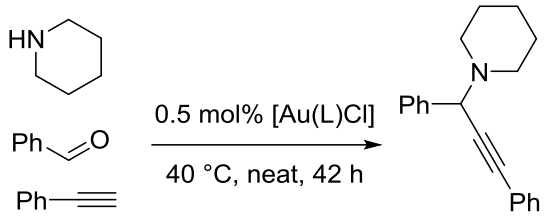
6). However, SPhos (**P-7**) was found to lead to very active catalysts for this transformation, as confirmed from profiling a model reaction. Notably, the poor performance of (electron-rich) triethylphosphine and electron-poor ligand **P-5** suggests that the difference in reactivity is not a simple electronic effect of the ligand; the steric profile of biarylphosphines may stabilise catalytic intermediates (see section 2.2).

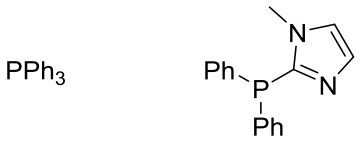
Scheme 4. Comparison of phosphine-ligated gold complexes in alkyne hydration. For the reactions in (a), catalysts were formed in situ from [AuCl(L)] and AgOTf and filtered before use. Conversions were obtained by GC analysis.



Several researchers have replaced aryl *P*-substituents with heteroaryl *P*-substituents. Wetzel *et al.* prepared a series of imidazol-2-yl and imidazol-4-ylphosphine ligands (**P-8** to **P-10**) and their corresponding gold complexes.[42] These were tested in the three-component coupling of benzaldehyde, piperidine, and phenylacetylene, and exhibited improved performance (up to 95% conversion with 0.5 mol% of gold catalyst) *versus* triphenylphosphine (26%) (Scheme 5) . However, their performance in the hydration of 1-octyne was generally very poor, with only one example coming close to the performance of triphenylphosphine.

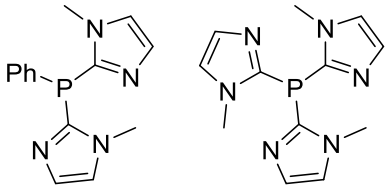
Scheme 5. Imidazolyl-substituted phosphine ligands in the gold-catalysed three component coupling reaction of benzaldehyde, piperidine, and phenylacetylene. Conversions were obtained by ^{1}H NMR integration.





P-1 26(3)%

P-8 70(2)%

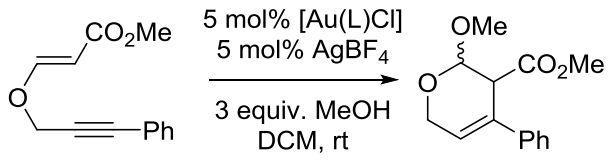


P-9 82(2)%

P-10 95(2)%

Matoušová *et al.* applied trifurylphosphine (**P-11**) in gold catalysis, and specifically for the synthesis of dihydropyrans (Scheme 6).[43] A comparison with a range of mono- and bidentate phosphines (**P-1**, **P-12**, and **P-13**) showed trifurylphosphine to be the most effective for this transformation. This efficacy is proposed to be due to its less electron-donating nature, improving the coordination of the cationic gold species to unsaturated carbon-carbon bonds; if this is the case, it is also likely to improve the electrophilicity of the corresponding gold-alkyne complex.

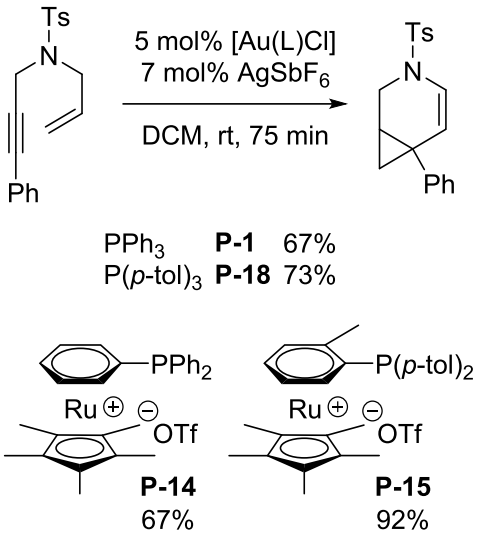
Scheme 6. Trifurylphosphine as a ligand for the gold-catalysed synthesis of dihydropyrans. The outcomes quoted are isolated yields.



PPh_3	**P-1**	58% *trans*	24% *cis*	1.5 h
PCy_3	**P-12**	46% *trans*	28% *cis*	1 h
dppe	**P-13**	54% *trans*	19% *cis*	16 h
$P(2\text{-fur})_3$	**P-11**	66% *trans*	32% *cis*	0.5 h

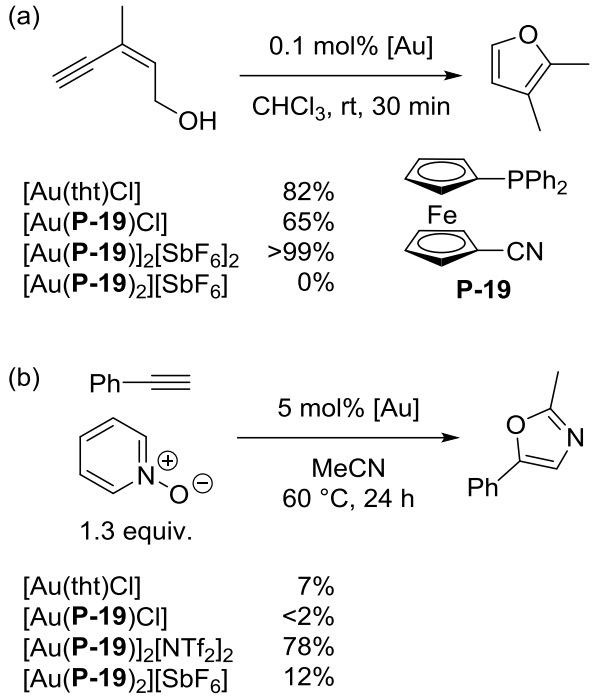
Dubarle-Offner *et al.* prepared phosphine ligands with three aryl substituents, of which one was coordinated to a $Ru(Cp^*)^+$ fragment.[44] It is well-known that coordination of this type has a considerable influence on the electronic properties of the arene. The new ligands (**P-14** and **P-15**) were prepared from the corresponding [Ru(Cp*)(η^2-ArCl)][OTf] complexes *via* an S_NAr reaction. Analysis of $\%V_{bur}$ data suggested that these ligands ($\%V_{bur}$ = *ca.* 43) had similar steric bulk to P(*t*-Bu)$_3$ (**P-6**) (*ca*. 44) or P(*o*-tol)$_3$ (**P-16**) (*ca.* 45) but less than $PMes_3$ (**P-17**) (*ca*. 51). Gold complexes of these ligands were tested in the cycloisomerisation of a 1,6-enyne substrate, typically showing improved performance *versus* the catalyst bearing P(*p*-tol)$_3$ (**P-18**) (Scheme 7).

Scheme 7. Triarylphosphine ligands with coordinated Ru(II) in the gold-catalysed cycloisomerisation reactions of 1,6-enynes. Conversions are quoted from ^{1}H NMR integration.



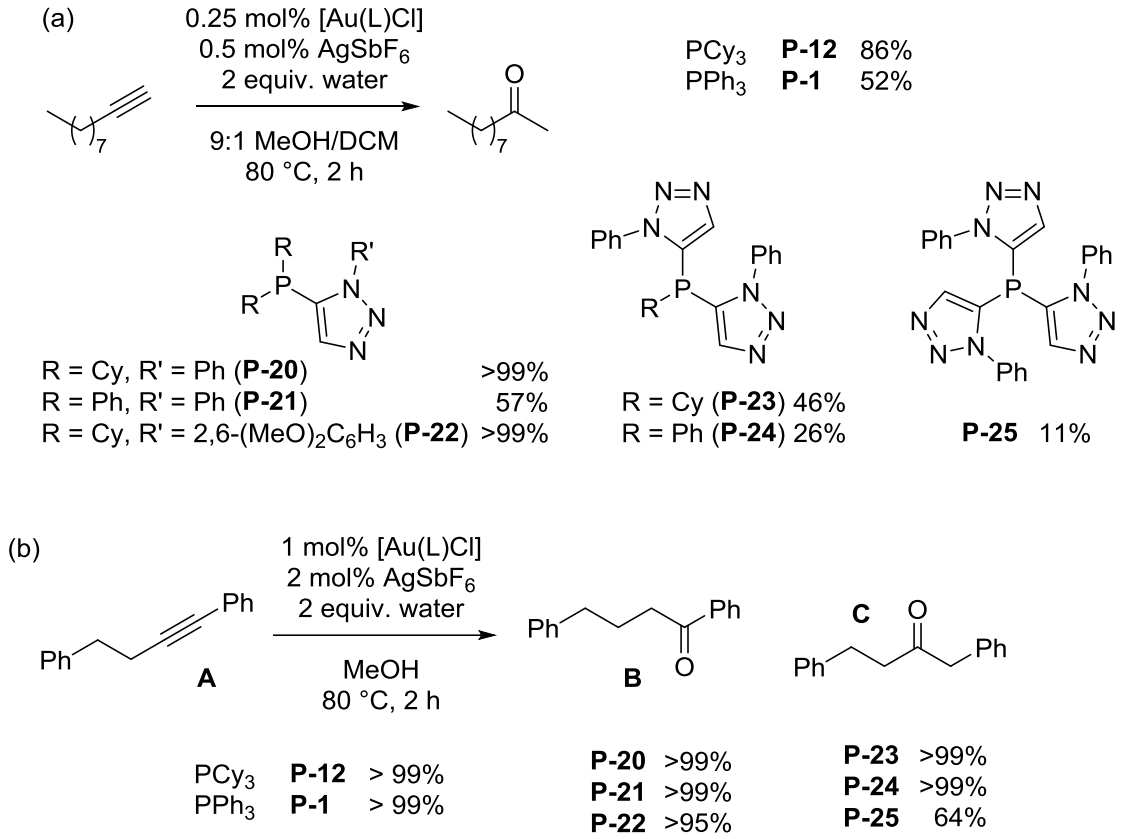
Škoch *et al.* prepared gold complexes of 1-cyano-1'-diphenylphosphinoferrocene (**P-19**) and applied them in some model catalytic reactions.[45] [Au(**P-19**)Cl], [Au(**P-19**)$_2$][X], [Au(**P-19**)(tht)][X], and [Au(**P-19**)]$_n$[X]$_n$ structures were obtained in various coordination chemistry experiments (X = Cl, NTf_2, SbF_6); the nitrile group is sufficiently coordinating to allow the formation of P-Au-N chains in the solid state. The resulting complexes were slightly more effective than [Au(tht)Cl] in the cyclisation of (*Z*)-3-methylpent-2-en-4-yn-1-ol to 2,3-dimethylfuran, but much more effective in the oxidative cyclisation of nitriles and alkynes to form oxazoles, where yields reached 88% (*versus* 0 – 7% for [Au(tht)Cl]) (Scheme 8). The presence of the nitrile functionality may act to stabilise catalytic intermediates.

Scheme 8. Testing of 1-cyano-1′-diphenylphosphinoferrocenes in gold catalysis. Conversions were determined by ^{1}H NMR integration.



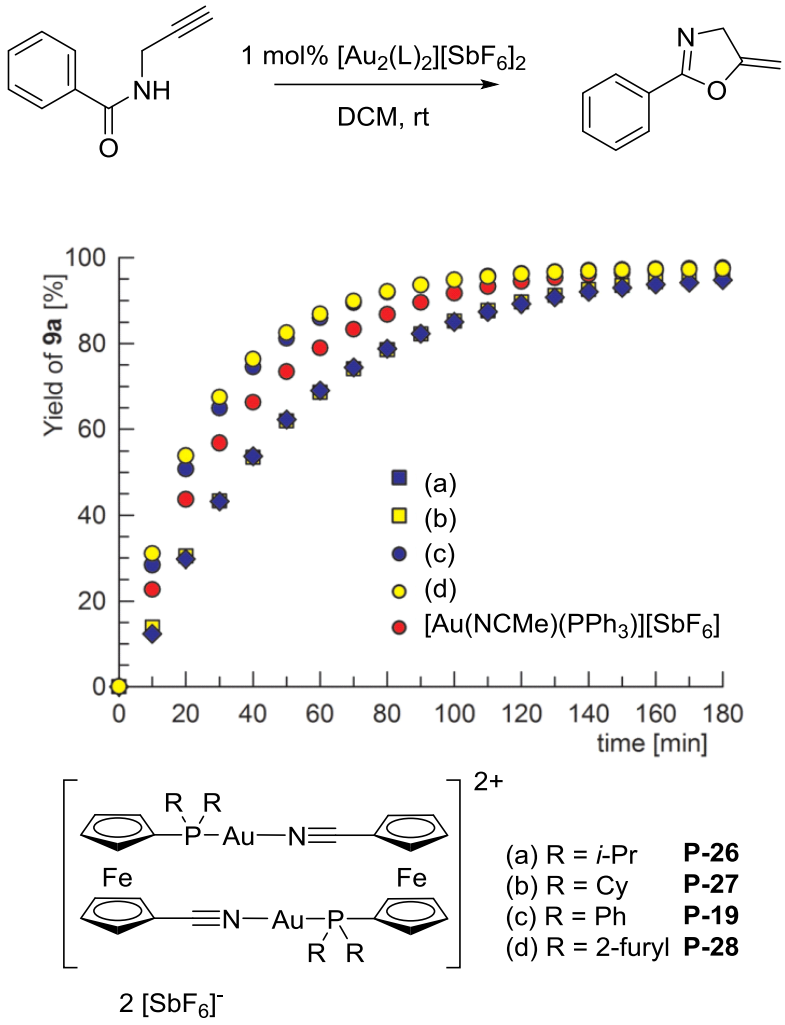
Zhao *et al.* have systematically assessed a series of 1-phenyl-5-phosphino-1,2,3-triazoles in gold catalysis;[46] these included species with various combinations of triazoles, phenyl groups, and cyclohexyl groups at the phosphorus (**P20** – **P-25**). The steric bulk of each ligand was measured using $\%V_{bur}$ analysis and topographical steric maps, and the ligands were tested in the hydration reactions of terminal (1-decyne) and internal (1,4-diphenylbut-1-yne) alkynes (Scheme 9). The most effective ligand was found to be one with two cyclohexyl groups and one triazole connected to phosphorus (**P-20**). It is possible that the bis(triazolyl)- and tris(triazolyl)phosphines are too electron-poor.

Scheme 9. Triazolylphosphines as ligands for gold-catalysed hydration reactions. Conversions were determined by NMR integration or GC analysis.



Bárta *et al.* prepared a series of 1-(dialkyl/diarylphosphino)-1'-cyanoferrocene ligands (**P-19** and **P-26 – P-28**) through the stepwise lithiation of 1,1'-dibromoferrocene.[47] Dimeric complexes of the form $[Au(\kappa^2\text{-}(N,P)\text{-}L)]_2[SbF_6]_2$ were formed from halide abstraction from the L-Au-Cl complexes, with each ligand coordinating one gold centre *via* the phosphine and one gold centre *via* the nitrile. These were assessed in the cyclisation reactions of propargylamides; kinetic profiles showed that the diphenylphosphino- and difurylphosphino-derivatives performed slightly better than $[Au(PPh_3)(NCMe)][SbF_6]$ (Scheme 10). Bulky, electron-rich *iso*-propyl and cyclohexyl substituents appeared to have a negative effect on catalytic performance.

Scheme 10. Ferrocene-based ligands for gold-catalysed cyclisation reactions. Conversions are determined by ^{1}H NMR integration. Adapted with permission from reference 47. Copyright 2019,The Royal Society of Chemistry.



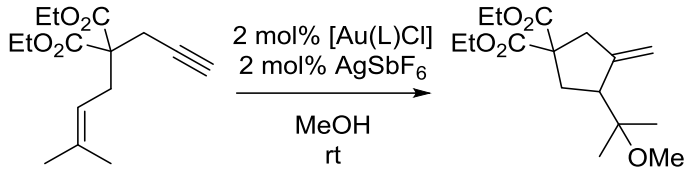
2.2 Biarylphosphines

(Biaryl)phosphine ligands – often referred to as 'Buchwald-type' ligands – were initially developed for a range of palladium-catalysed cross-coupling reactions but have since been found to be particularly effective ligands for a range of gold-mediated processes. These ligands have been extensively evaluated for a number of transformations and serve as inspiration for further classes of ligand that are discussed subsequently in this review. The steric profile of these ligands places an aryl group in close proximity to the metal centre, which has been proposed to influence reactivity but also to aid catalyst stability.

In an early study on the use of biarylphosphines in gold catalysis, Nieto-Oberhuber *et al.* noted that Cy-JohnPhos (**P-29**), JohnPhos (**P-30**), XPhos (**P-31**), and SPhos (**P-7**) were all highly effective

ligands for the gold-catalysed cycloisomerisation of 1,3-enynes (Scheme 11).[48] It was noted that catalysts bearing these ligands outperformed those with triarylphosphines or NHC ligands.

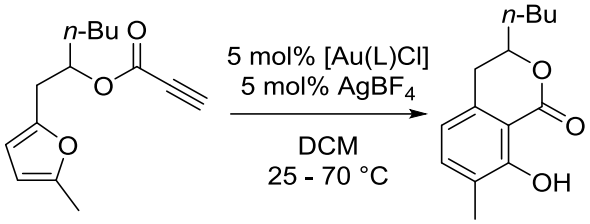
Scheme 11. Catalyst screening for the cycloisomerisation reactions of 1,3-enynes.



L = PPh_3 (**P-1**)	84% yield, 3 h
L = P(*o*-tol)$_3$ (**P-16**)	90% yield, 24 h
L = CyJohnPhos (**P-29**)	97% yield, 0.5 h
L = JohnPhos (**P-30**)	90% yield, 0.25 h
L = XPhos (**P-31**)	92% yield, 0.25 h
L = SPhos (**P-7**)	89% yield, 0.25 h
L = IMes (**NHC-3**)	71% yield, 1.5 h

Hashmi *et al.* have screened a variety of gold complexes for the Hashmi phenol synthesis of isocoumarins from furans (Scheme 12).[49] These included triphenylphosphine (**P-1**), alkyldiadamantylphosphine ligands (e.g. benzyldiadamantylphosphine (**P-32**), tri(*tert*-butyl)phosphine (**P-6**), and JohnPhos (**P-30**), DavePhos (**P-33**), SPhos (**P-7**), RuPhos (**P-34**), and XPhos (**P-31**) (*inter alia*). Only (biaryl)phosphines were found to be effective, with other classes of ligand failing to yield product. A systematic and quantitative comparison of ligands is somewhat difficult, as the benchmark reactions were not all performed over the same time period at the same temperature; however Me_4*t*-BuXPhos appears to be the most effective ligand. The requirement for a (biaryl)phosphine was proposed to be due to the need for a gold-arene contact, which is present in all of the ligands with a biaryl-substituent on the phosphine. Again, this may serve to stabilise the active species and prevent the formation of, for example, gold nanoparticles.

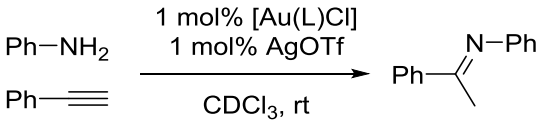
Scheme 12. Catalyst screening for the Hashmi phenol synthesis. Conversions are determined by ^{1}H NMR integration.



L = no ligand	0%
L = P*t*Bu$_3$ (**P-6**)	0%
L = BnPAd$_2$ (**P-32**)	0%
L = JohnPhos (**P-30**)	57%
L = Me$_4$*t*-BuXPhos (**P-35**)	75% (3 d)
L = CyJohnPhos (**P-29**)	67% (5 d)
L = DavePhos (**P-33**)	64% (6 d)
L = SPhos (**P-7**)	58% (4 d)
L = RuPhos (**P-34**)	50% (6 d)
L = XPhos (**P-31**)	65% (14 d)
L = *t*-BuXPhos (**P-36**)	44% (10 d)
L = TrixiePhos (**P-37**)	68% (5 d)

Malhotra *et al.* have conducted a systematic comparison of various phosphine ligands for the hydroamination of phenylacetylene with aniline (Table 1).[50] An electron-deficient XPhos analogue (**P-38**) performed poorly, with XPhos (**P-31**), and JohnPhos (**P-30**) performing moderately well. However, the most effective ligand was found to be a new ligand "BiPhePhos" (CyP{*o*-(2,6-(*i*-PrO)C$_6$H$_3$)C$_6$H$_4$}$_2$) (**P-39**). It should be noted here that IPr (**NHC-1**) is not the most effective ligand for hydroamination, and that CAACs can often be much better ligands for this type of gold-catalysed transformation (see section 3.4). The efficiency of **P-39** as a ligand for gold catalysis is proposed to be due to the steric bulk disfavouring the formation of *gem*-diaurated intermediates. A thorough evaluation of gold complexes of **P-39** established that it was more effective than the corresponding triphenylphosphine complexes for a range of transformations, and at significantly lower catalyst loadings.

Table 1. Relative rates for the hydroamination of phenylacetylene with aniline, using an [Au(L)Cl] pre-catalyst and AgOTf (1 mol% of each) in $CDCl_3$ at room temperature.

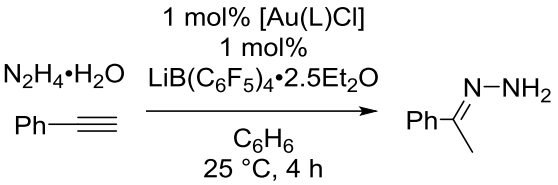


Ligand	Rel. rate
(3,5-(CF$_3$)$_2$C$_6$H$_3$)XPhos (**P-38**)	0.01
QPhos (**P-40**)	0.40
(2'-biphenyl)$_3$P (**P-41**)	0.72
IPr (**NHC-1**)	1.0
PhXPhos (**P-42**)	1.2

Me_3(MeO)XPhos (**P-43**)	2.5
XPhos (**P-31**)	3.0
(2'-biphenyl)$_2$PCy (**P-44**)	3.2
t-BuXPhos (**P-36**)	4.1
SPhos (**P-7**)	4.1
BrettPhos (**P-45**)	5.4
JohnPhos (**P-30**)	5.6
BiPhePhos (**P-39**)	9.0

Rotta-Loria *et al.* have screened a variety of ligands in the gold-catalysed hydrohydrazination of terminal alkynes (Scheme 13).[51] Various Buchwald-type (JohnPhos (**P-30**), AdJohnPhos (**P-46**), DalPhos (PAd-Dalphos (**P-47**), Mor-DalPhos (**P-48**), OTIPS-DalPhos (**P-49**)) and other phosphines (BippyPhos (**P-50**), cataCXium-A (**P-51**)) were screened in this reaction. CataCXium-A (*n*-BuPAd$_2$) (**P-51**) was found to be particularly effective, allowing the reaction to proceed efficiently with a typical 1 mol% catalyst loading in benzene at 25 °C for 4 hours.

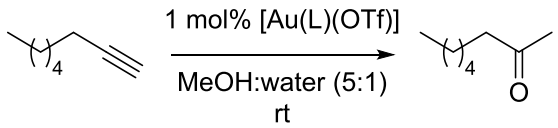
Scheme 13. Catalyst screening for hydrohydrazination.



L = BippyPhos	**P-50**	<10%
L = JohnPhos	**P-30**	20%
L = AdJohnPhos	**P-46**	60%
L = OTIPS-DalPhos	**P-49**	20%
L = (*t*Bu$_3$SiO)DalPhos	**P-52**	90%
L = cataCXium-A	**P-51**	>95%
L = Mor-DalPhos	**P-48**	<10%
L = PAd-DalPhos	**P-47**	<10%

Ebule *et al.* have profiled the hydration of 1-octyne with a series of [Au(L)OTf] complexes, with a focus on Buchwald-type phosphines (Scheme 14).[52] Me_3(OMe)*t*-BuXPhos (**P-43**) performed best, followed by *t*-BuXPhos (**P-36**); JohnPhos (**P-30**), SPhos (**P-7**), XPhos (**P-36**), and PhXPhos (**P-42**) performed similarly to IPr (**NHC-1**), as did an electron-deficient XPhos analogue with 3,5-bis(trifluoromethyl)phenyl *P*-substituents (**P-38**). PhJohnPhos (**P-53**) gave a poor catalyst which was only slightly more reactive than [Au(P(OPh)$_3$)(OTf)]. This is a rather different order of reactivity to that observed for hydroamination, where JohnPhos (**P-30**) gave one of the more effective catalysts. Relative rates were not quoted numerically, but reaction profiles over 1 to 30 h give a good indication of the relative reactivity of each pre-catalyst. [Au((MeO)Me_3XPhos)(OTf)] gave full conversion in only 2 – 3 hours, while most catalysts took 24 h or longer to reach full conversion.

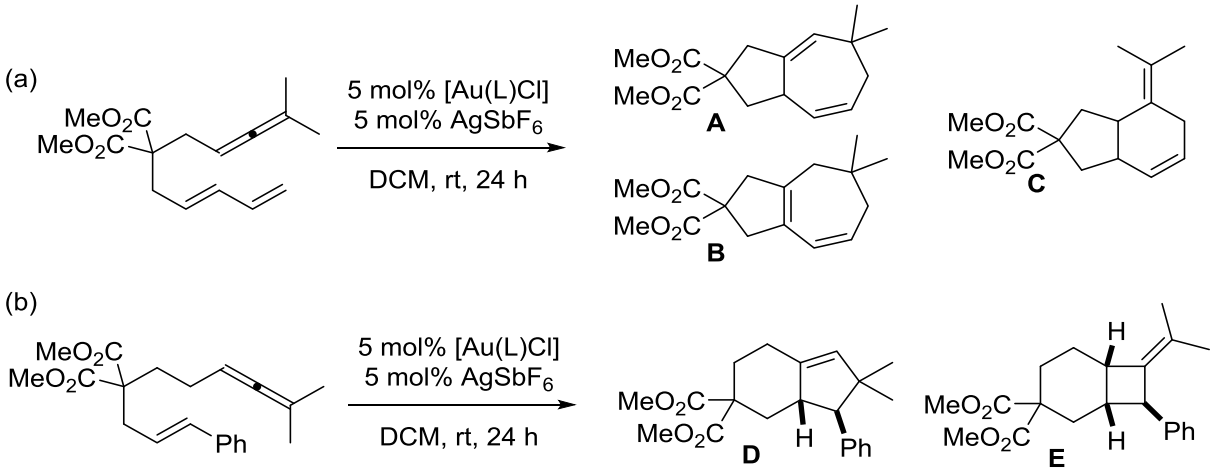
Scheme 14. Catalyst screening for alkyne hydration.



Reaction rate:
(MeO)Me_3XPhos (**P-43**) > *t*-BuXPhos (**P-36**) > IPr (**NHC-1**) ~ SPhos (**P-7**) ~ JohnPhos (**P-30**) > PhJohnPhos (**P-53**) > $P(OPh)_3$ (**P-54**)

Christian *et al.* have used linear regression analysis to explore the effect of phosphine ligand structure on reactivity in gold catalysis, using [4+3]/[4+2] and [2+3]/[2+2] cyclisation reactions as model reactions (Scheme 15 (a)).[53] In the former reaction, the measured selectivity for products **A** and **B** *vs* product **C** (expressed as $\Delta\Delta G^{‡}$) correlated well with the measured Au-Cl bond distance in the pre-catalyst (Figure 2 (a)). In contrast, the selectivity for product **D** *versus* product **E** in the [2+3]/[2+2] cyclisation reaction was not strongly correlated, and instead it was found that a Sterimol L/B_1 descriptor, representing the steric size of the ligand, gave a much better correlation (Scheme 15 (b) and Figure 2 (b)). This information suggested that the mechanisms of the two reactions were rather different, and allowed the selection of a new ligand (di(*tert*-butyl)(4-terphenyl)phosphine) (**P-55**) which was predicted to show 31:1 selectivity ($\Delta\Delta G^{‡}$ = 2.0 kcal/mol) and experimentally showed 17:1 selectivity ($\Delta\Delta G^{‡}$ = 1.7 kcal/mol), which is very good agreement.

Scheme 15. Model reaction for linear regression analysis of (a) [4+3]/[4+2] and (b) [2+3]/[2+2] cycloisomerisation reactions.



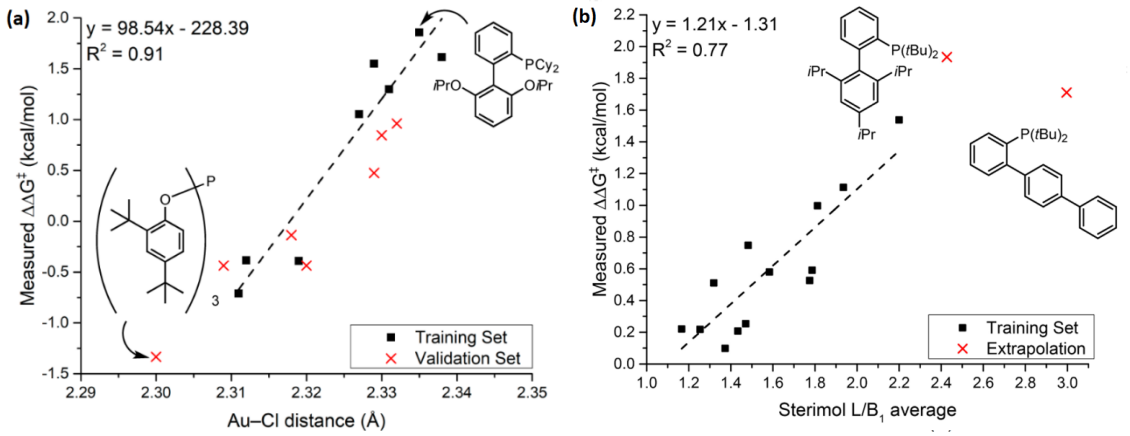
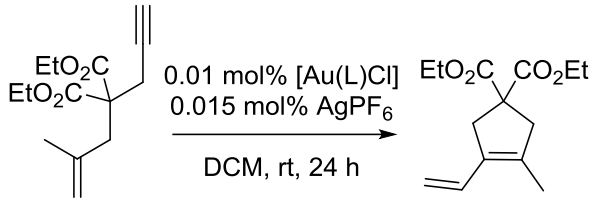


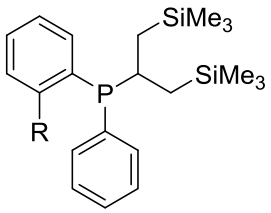
Figure 2. Correlations between (a) selectivity for **C** over **A** plus **B** versus Au-Cl distance in the corresponding pre-catalyst and (b) selectivity for **D** over **E** versus the Sterimol L/B_1 parameter. Reproduced with permission from reference 52. Copyright (2017) American Chemical Society

Mahamulkar *et al.* designed and prepared a series of alkyl(2'-biphenyl)phenylphosphine ligands (**P-56**, **P-57**, and **P-58**) and evaluated these in gold-catalysed reactions.[54] Several of these are somewhat analogous to Buchwald-type ligands except for the replacement of one alkyl *P*-substituent with a phenyl group. Catalysts with these new ligands were compared to the corresponding JohnPhos (**P-30**) catalyst in the cyclisation reactions of 1,6-enynes at very low catalyst loadings (0.01 mol%); several of the new ligands offered somewhat better performance than JohnPhos (Scheme 16).

Scheme 16. Catalytic testing of new phosphine ligands. Results are quoted as conversion determined by ^{1}H NMR spectroscopy.



JohnPhos (**P-27**): 87% (1650 min)



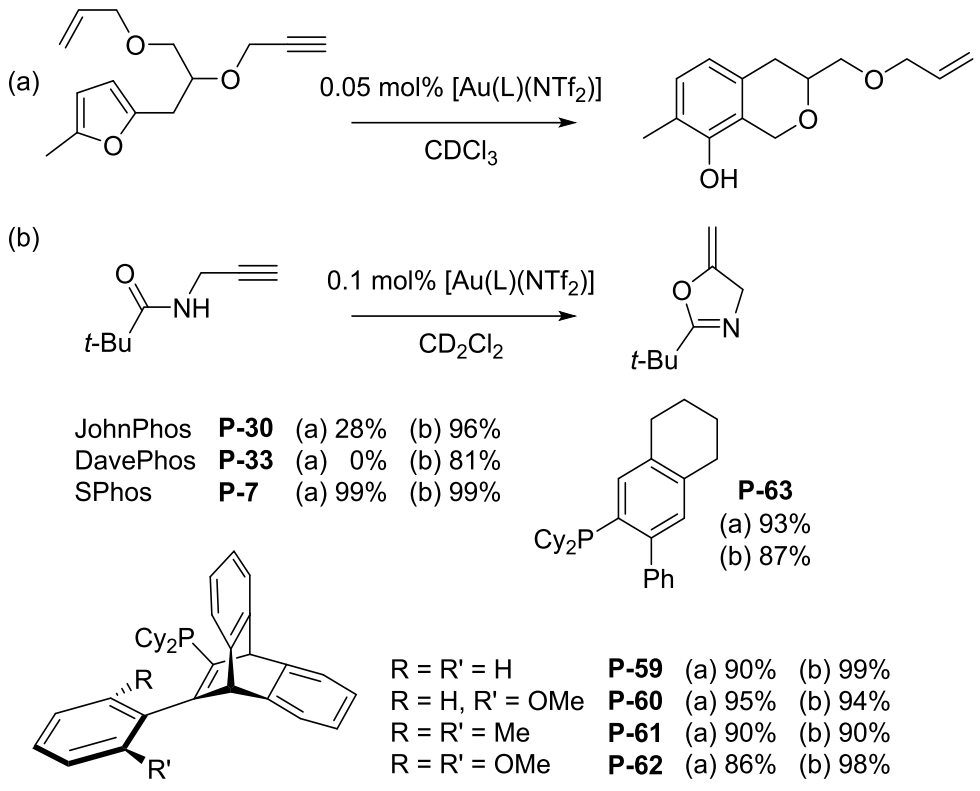
R = $CHPh_2$	**P-56**	85%	1470 min
R = Ph	**P-57**	100%	1185 min
R = CH_2CH_2Ph	**P-58**	10%	1290 min

2.3 KITPHOS Ligands

KITPHOS-type ligands have been applied in several studies of gold catalysis. These are typically prepared from cycloaddition reactions between alkynes and anthracenes[55] and are rather less flat than many of the common Buchwald-type ligands. They therefore offer opportunities to confer different steric profiles on the corresponding gold catalysts.

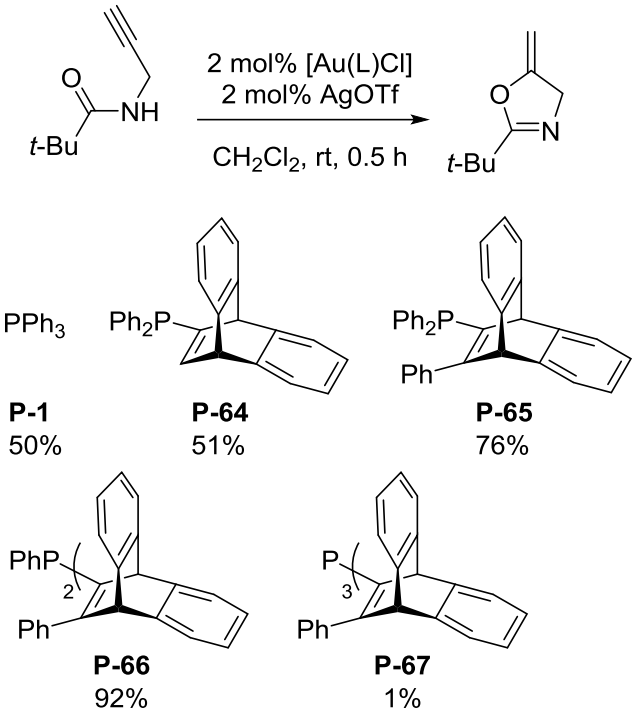
Hashmi *et al.* have prepared KITPHOS gold complexes and compared them to JohnPhos (**P-30**) and DavePhos (**P-33**) in some model catalytic reactions, including the Hashmi phenol synthesis and various intramolecular allene and alkyne functionalisation reactions.[56,57] The complexes with new ligands (**P-59** to **P-62**) tended to outperform complexes of Buchwald-type ligands in the Hashmi phenol synthesis and were comparable in reactions such as the cyclisation of alkynes or allenes with pendant amide, alcohol, or carboxylic acid substituents (Scheme 17); however, yields were generally very good for reactions of the latter type, regardless of the ligand choice. Further examples of this class of ligand were reported by Hashmi *et al.* in which alternative substitution patterns were explored and tested in the same palette of model reactions *versus* some Buchwald-type ligands.[58]

Scheme 17. Catalytic testing of KITPHOS ligands. Results are quoted as conversion determined by integration of the ^{1}H NMR spectrum versus an internal standard.



Doherty *et al.* prepared a series of ligands (**P-64** – **P-67**) with various numbers of dihydroanthracene-derived substituents and tested the corresponding gold complexes in gold-catalysed cyclisation reactions (Scheme 18).[59] The dihydroanthracene fragments are very sterically large, and so for the corresponding [Au(L)Cl] complexes $\%V_{bur}$ values of up to 64.5% were measured; this exceeds $\%V_{bur}$ for $PMes_3$ (45.0), $P(o\text{-tol})_3$ (39.4), and even for $P(TBDMS)_3$ (58.7). In the cyclisation reactions of propargylamides, the bis-KITPHOS ligand (**P-66**) often outperformed the mono-KITPHOS ligand (**P-65**), and both outperformed triphenylphosphine; however, the tris-KITPHOS ligand (**P-67**) led to poor yields (≤ 24% across five reactions). Similar results were obtained for the cyclisation reactions of 2-alkynylbenzyl alcohols. There is therefore clearly a practical limit in how bulky these ligands can be before they impede productive catalysis, and this lies somewhere between two and three dihydroanthracene-derived *P*-substituents.

Scheme 18. Catalytic testing of mono-, bis-, and tris-KITPHOS ligands. Results are quoted as isolated yields.

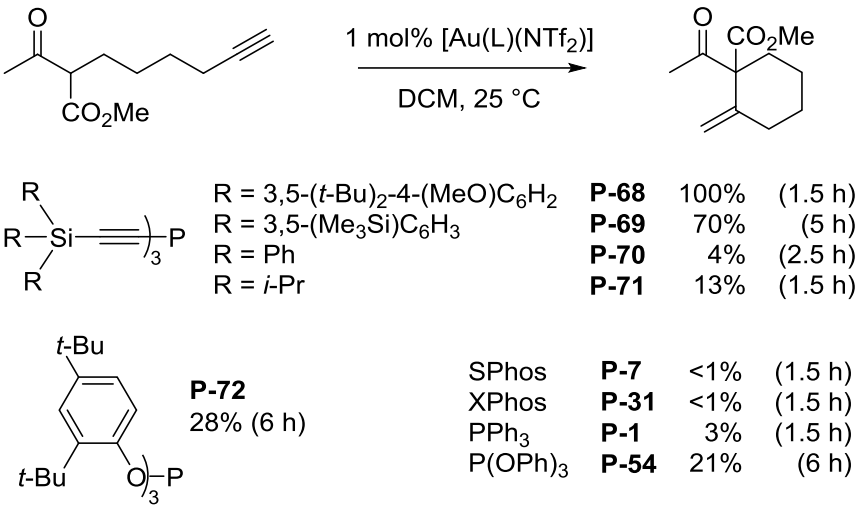


2.4 Trialkynylphosphines

Ochida *et al.* prepared very large $P(CCSiAr)_3$ ligands and evaluated these for the gold-catalysed cyclisation of ketoesters with pendant alkyne groups, and for the cyclisation reactions of 1,7-enynes (Scheme 19).[60] The new ligand was significantly more effective for the former reactions than bulky triarylphosphites, triphenylphosphine, JohnPhos, or SPhos. The hypothesis is that this very bulky ligand architecture creates a cavity around the gold-alkyne or gold-alkene complex, promoting ring-

closing *anti*-attack. Ligands of this sheer size will have an influence on the secondary coordination sphere, which provides another interesting vector for ligand design.

Scheme 19. Catalytic testing of very bulky trialkynylphosphines.



2.5 Strongly Electron-Deficient Phosphorus Ligands

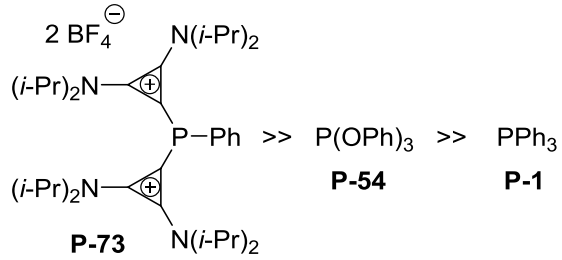
While in many fields, such as palladium catalysis, researchers have sought to design and apply more electron-rich ligand systems, for some gold catalysed reactions electron-deficient ligands can be more effective. In theory, electron-deficient ancillary ligands should lead to more electrophilic gold-alkene, gold-allene, and gold-alkyne complexes; less electron-rich gold catalysts should promote the $\pi \rightarrow d$ component of the Dewar-Chatt-Duncanson model for the coordination of metals to π-systems, and this thinking has led to the use of ligands such as triarylphosphites in gold catalysis. The field of α-cationic phosphines, which are another key class of compounds in this area of ligand design, has recently been reviewed by Alcarazo.[61]

Carreras *et al.* have prepared gold complexes with cationic cyclopropenium substituents on the phosphorus ligand, which then formally bears a positive charge (Scheme 20).[62] This new ligand (**P-73**) is approximately as bulky as tri(*tert*-butyl)phosphine (**P-6**), but as electron-donating as $P(CF_3)_3$ as judged from the measurement of the Tolman Cone Angle and the Tolman electronic parameter. This new ligand was found to be very effective for the intramolecular hydroarylation reactions of a range of substrates, with yields typically exceeding 90% when 2 mol% [Au(L)Cl] was used with 2 mol% of $AgSbF_6$. Reaction profiles were used to compare the new ligand (**P-73**) with triphenylphosphine (**P-1**) and triphenylphosphite (**P-54**); the catalyst system using **P-73** achieved full conversion in 10 minutes, while the triphenylphosphite complex achieved only 30% conversion after 30 minutes. The triphenylphosphine-bearing catalyst was very poor for this reaction, with less than 10% conversion

after 30 minutes. Despite the intramolecular nature of this reaction, which should promote the nucleophilic attack of the intermediate gold-alkyne complex, the reaction requires a very electron-poor catalyst; this is consistent with a rate-determining nucleophilic attack step.

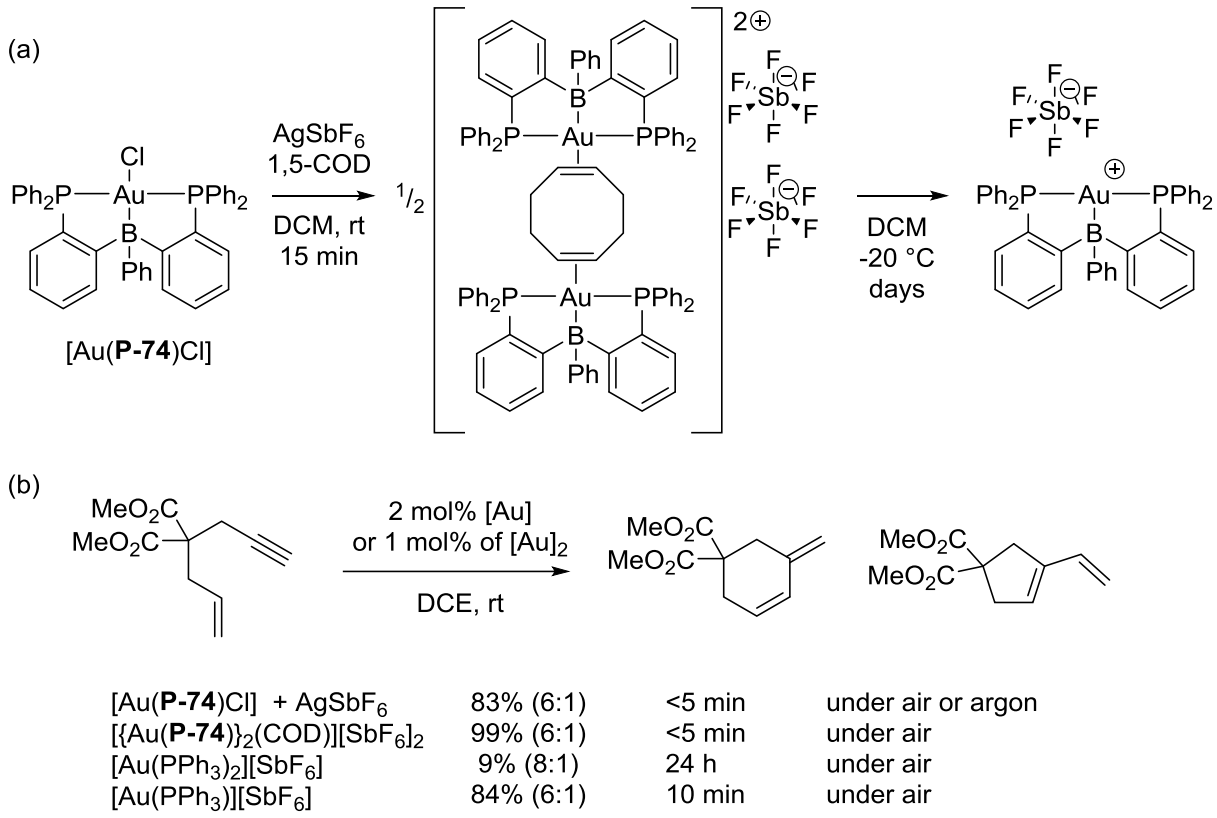
Scheme 20. Cationic phosphine complexes for intramolecular hydroarylation.

Reaction rate:



Inagaki *et al.* prepared gold complexes of bis(2-diphenylphosphinophenyl)phenylborane (DPB, **P-74**) (Scheme 21).[63] This Z-type supporting ligand allowed an air-stable cationic gold species to be isolated and characterised (Scheme 21 (a)). These complexes were compared to $[Au(PPh_3)_2][SbF_6]$ and $[Au(PPh_3)][SbF_6]$ in the cyclisation reactions of enynes. One of these complexes, $[\{Au(DPB)\}_2(COD)][SbF_6]_2$, was found to be much more effective than $[Au(PPh_3)_2][SbF_6]$ and somewhat more effective than $[Au(PPh_3)][SbF_6]$ across a range of these enyne cyclisation reactions (Scheme 21). In addition, it also outperformed cationic gold complexes of XPhos (**P-31**) in these reactions.

Scheme 21. Z-type ligands support catalysts for enyne cycloisomerisation reactions. Yields are isolated yields, with product ratios determined by ^{1}H NMR integration.

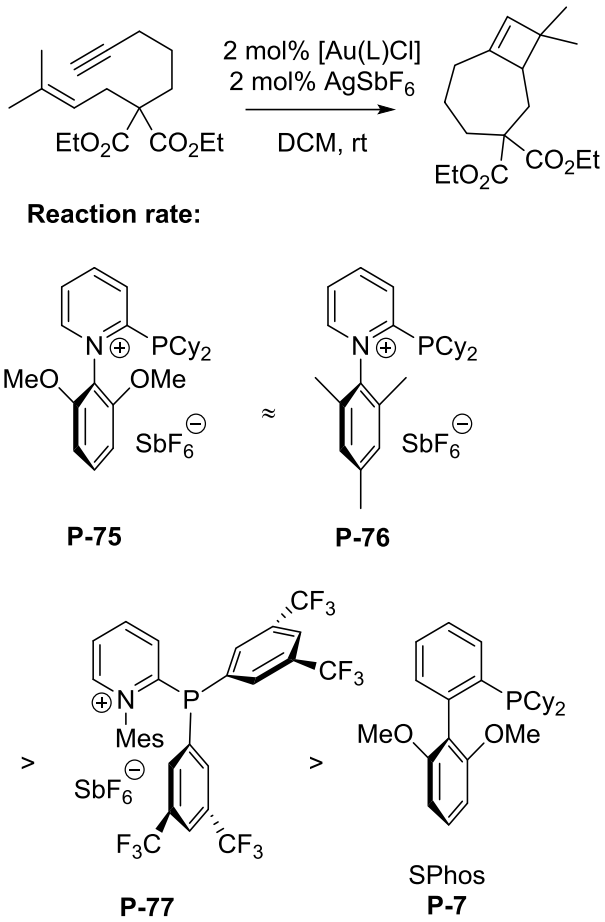


[Au(**P-74**)Cl] + $AgSbF_6$	83% (6:1)	<5 min	under air or argon
[{Au(**P-74**)}$_2$(COD)][SbF_6]$_2$	99% (6:1)	<5 min	under air
[$Au(PPh_3)_2$][SbF_6]	9% (8:1)	24 h	under air
[$Au(PPh_3)$][SbF_6]	84% (6:1)	10 min	under air

Tinnermann *et al.* have prepared *N*-arylpyridiniophoshines (**P-75**, **P-76**, and **P-77**), which are charged analogues of Buchwald-type phosphine ligands in which the quaternary carbon β to the phosphine is replaced with a nitrogen (Scheme 22).[64] This allows these ligands to retain essentially the same steric profile as the corresponding (biaryl)phosphines while significantly changing their electronic properties. These were characterised using crystallographic and electrochemical methods, allowing $\%V_{bur}$ and E_p to be determined; the TEP could not be measured, because attempts to synthesise the requisite [IrCl(COD)(L)] species *en route* to [$IrCl(CO)_2$(L)] complexes led to interesting but problematic spontaneous aryl C-H oxidative addition. Electrochemical studies indicated a significant decrease in the basicity of the ligands compared to their Buchwald-type analogues, which is unsurprisingly given the electron-poor nature of the pyridinium *P*-substituent. Catalytic tests including time profiles for the cycloisomerisation of an enyne to a cyclobutene showed a significant rate enhancement for these new ligands *versus* a prototypical Buchwald-type ligand (SPhos, **P-7**) (Scheme 22). These new ligands also outperformed SPhos (**P-7**), triphenylphosphine (**P-1**), and triphenylphosphite (**P-54**) for the intramolecular hydroarylation reaction to form [6]helicenes. Once again, despite the intramolecular nature of the nucleophilic attack step – which in some other

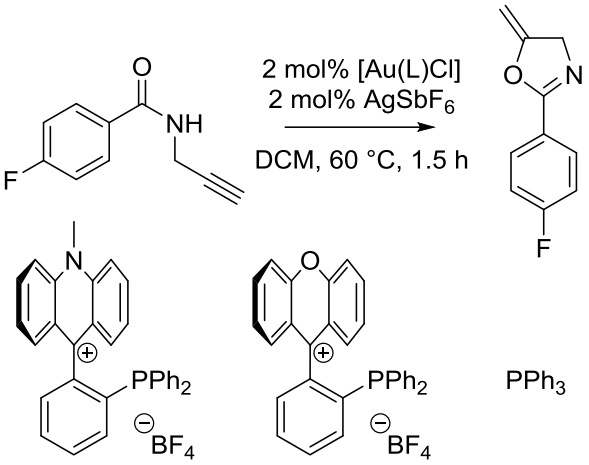
reactions means that a different step becomes rate-determining – the use of electron-poor ligand significant increases the rate of reaction by increasing the reactivity of the gold-alkyne intermediate.

Scheme 22. Enyne cycloaddition catalysed by N-arylpyridiniophoshine-gold(I) complexes.



Wilkins *et al.* have prepared a ligand framework, which bears some similarities to the core of most Buchwald-type phosphine ligands, in which a stabilised carbenium is placed in close proximity to the gold centre.[65] QTAIM calculations were used to confirm that an interaction between the gold centre and the carbenium ion was present. Catalytic testing using a model cyclisation reaction of a propargylamide showed a significant difference in performance between these new ligands and triphenylphosphine (Scheme 23). The positive charge is in conjugation with the aryl *P*-substituent and so will influence its electronic character but the C…Au interaction identified computationally suggests that the difference in catalytic performance may be due to more than a simple change in electron-density at the phosphorus ligand.

Scheme 23. Ligands with stabilised carbenium substituents in gold catalysis. Conversion determined by ^{19}F NMR spectroscopic analysis.



P-78 52%

P-79 97%

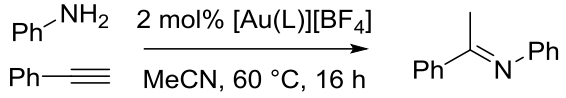
P-1 0%

2.6 Strongly Electron-Donating Phosphorus Ligands

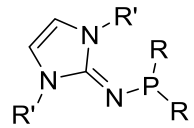
While alkylphosphines are among the more electron-donating phosphorus ligands, a series of more electron-rich phosphorus ligands have been developed. Two such classes of ligands have been applied to gold catalysis and so are described here. Both studies deploy hydroamination as a model reaction.

Witteler *et al.* prepared and studied a series of dialkyl(1,3-diarylimidazolin-2-ylideneamino)phosphines (**P-80** – **P-84**), reasoning that these would provide a similar steric profile to 'Buchwald-type' ligands while being rather more electron rich (Scheme 24).[66] The evaluation of TEP shows that these species can in fact be more electron-donating than many *N*-heterocyclic carbenes, and are more electron rich than typical trialkylphosphines such as P(*i*-Pr)$_3$ or P(*t*-Bu)$_3$.[67] %V_{bur} were calculated for DFT-derived structures of the corresponding gold complexes, and found to be higher than 50% in most cases, and over 60% for the corresponding cationic L-Au$^+$ species. The new ligands were compared to triphenylphosphine and JohnPhos (**P-30**) in three model hydroamination reactions, with **P-80** offering performance (85 – 97%) that is typically on par with JohnPhos (85 – 98%), and significantly better than PPh_3 (3 – 30%).

Scheme 24. Electron-rich ligands for gold-catalysed hydroamination reactions. The complexes were prepared from the corresponding [Au(L)Cl] complexes and $AgBF_4$, and filtered through glass wool.



JohnPhos	**P-30**	85%
PPh_3	**P-1**	7%

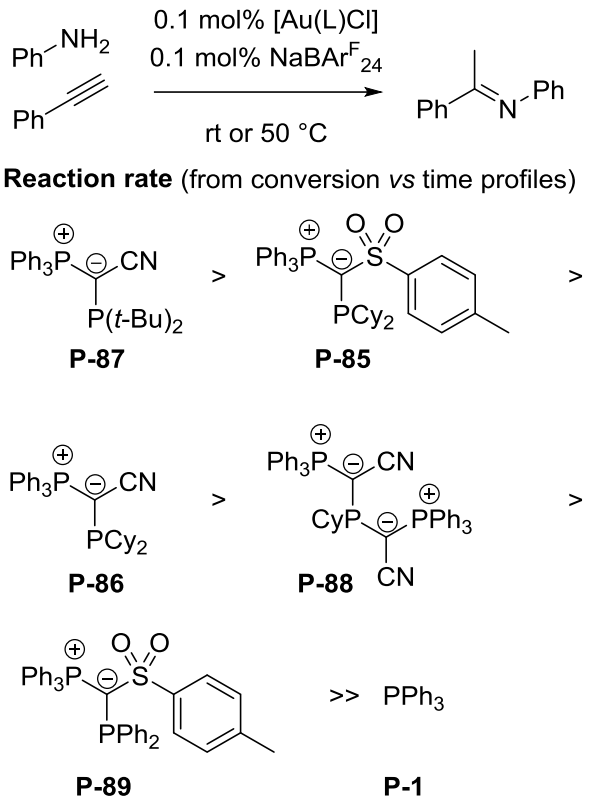


R = *t*-Bu	R' = Mes	**P-80**	85%
R = *t*-Bu	R' = 2,6-(*i*-Pr)$_2$C$_6$H$_3$	**P-81**	72%
R = *i*-Pr	R' = Mes	**P-82**	67%
R = *i*-Pr	R' = 2,6-(*i*-Pr)$_2$C$_6$H$_3$	**P-83**	71%
R = *i*-Pr	R' = *i*-Pr	**P-84**	45%

Phosphine ligands with ylide substituents are a relatively recent development in ligand design for gold catalysis, and for other areas such as palladium-catalysed cross-coupling. Two key studies from Gessner's laboratory are discussed here.

Scherpf *et al.* have prepared gold complexes of strongly electron-donating ylide-functionalised phosphines and applied these in a model hydroamination reaction using phenylacetylene and aniline (Scheme 25).[68] The reactions were monitored over approximately 24 hours. Triphenylphosphine (**P-1**) gave only *ca.* 30% conversion, while TsC(PCy_2)(PPh_3) (**P-85**) enabled essentially complete conversion within six hours, and NCC(PCy_2)(PPh_3) (**P-86**) gave *ca.* 85% conversion after six hours. The scope of the hydroamination reaction was studied further, and a total of eight examples were reported with yields of 94 – 99% using catalyst loadings of 0.1 – 0.2 mol% at 50 – 80 °C over the course of 6 to 48 h. Low loadings of the catalyst (0.1 to 0.5 mol%) were also able to catalyse intramolecular hydrocarboxylation, phenylacetylene hydration, and the formal [2+2] cycloaddition of α-methylstyrene and phenylacetylene. Schwarz *et al.* subsequently designed, prepared, and tested a larger suite of these "YPhos" ligands.[69] Examples have been prepared with one or two ylidic substituents, and different substitution patterns elsewhere in the ligand. These form particularly electron-rich ligands which can enable room-temperature intermolecular hydroamination reactions within only 0.1 mol% of [Au(YPhos)Cl] plus 0.1 mol% $NaBAr^F_{24}$. The study includes the full characterisation of the ligands by TEP and buried volume analysis, and reaction profiles for the hydroamination reactions catalysed by various [Au(YPhos)Cl] complexes. In general, the ligands with one ylidic substituent gave more active catalysts than those with two, with new ligand NCC(P(*t*-Bu)$_2$)(PPh_3) (**P-87**) providing the most active catalyst.

Scheme 25. Evaluation of YPhos ligands for alkyne hydroamination. Rate data are qualitative and based on NMR integration of samples withdrawn at timepoints



The precise step in the hydroamination mechanism that benefits from these more electron-rich ligands has not been clearly identified, although it is unlikely that it is the nucleophilic attack step, as this should benefit from *electron-poor* ligands as discussed in the preceding section of this review. Instead, these electron-donating ligands may be accelerating the protodeauration step, or stabilising the catalytic intermediates and thereby decreasing the rate of catalyst decomposition.

2.7 Phosphorus Ligands with Basic Amine Functional Groups

A range of phosphorus ligands with an additional basic amine functionality has been reported in the gold catalysis literature. In general, these ligands rely on presenting this functionality to allow important secondary interactions or processes to take place and lower the barrier to key steps in gold-catalysed reactions. The group of Zhang has been particularly active in this area of gold catalysis, focussing on the hydrogen bond accepting behaviour that can be engineered, although the inclusion of basic amine groups within ligands has been achieved in ligands such as DavePhos and Mor-DalPhos.

Hesp and Stradiotto noted that phosphine ligands with an *o*-(dialkyamino)aryl substituent and two bulky electron rich alkyl substituents led to significant improvements in the performance of gold-catalysed hydroamination reactions.[70] The best performance was observed with Mor-DalPhos (**P-48**), which allowed the hydroamination of a large number of alkynes with primary and secondary amines (Figure 3 is taken from the paper).

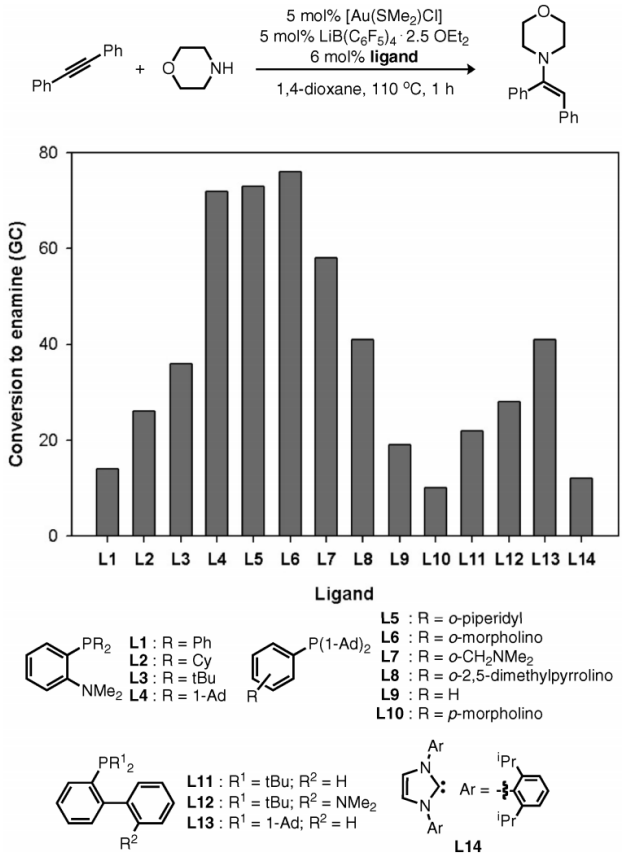
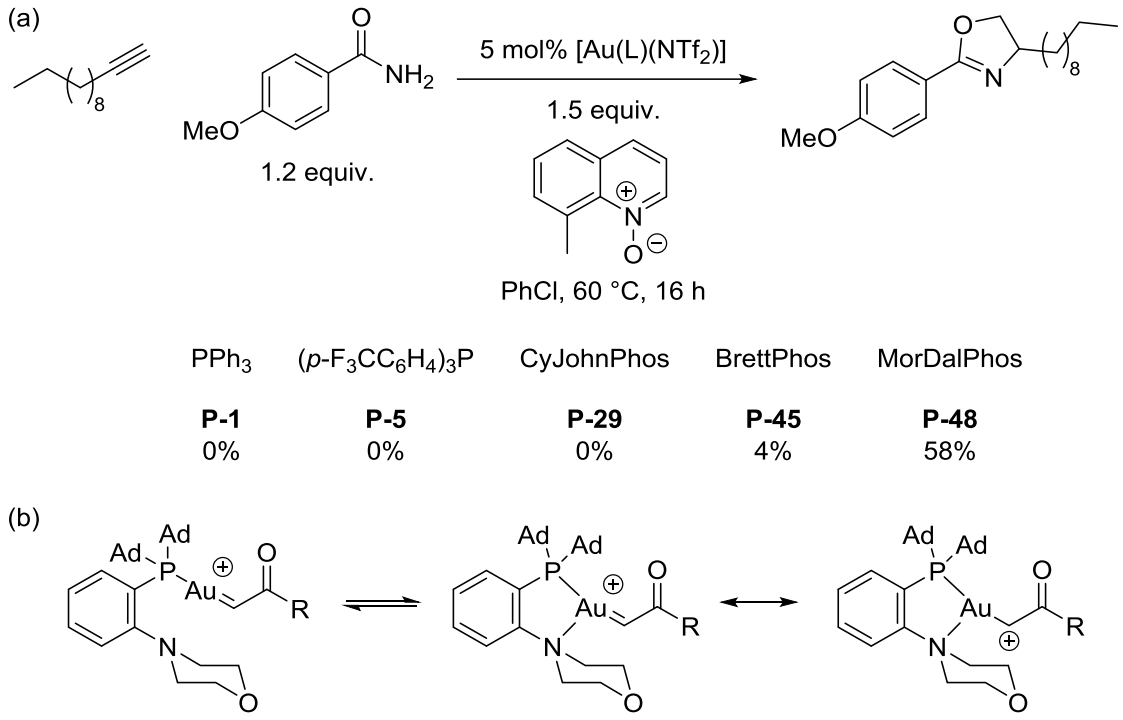


Figure 3. Mor-DalPhos for the hydroamination of alkynes. Conversions determined by GC. Image reproduced with permission from reference 68. Copyright (2010) American Chemical Society.

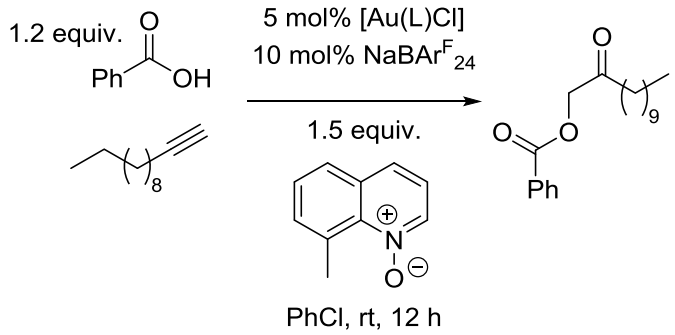
Luo *et al.* noted that MorDalPhos (**P-48**) gave a particularly active catalyst for the synthesis of oxazoles from amides and alkynes (Scheme 25 (a)).[71] These reactions proceed through the oxidation of the alkyne to form a gold-carbene (or gold-stabilised carbenium) intermediate which is then attacked by the amide substrate. It was proposed that MorDalPhos (**P-48**) promoted this reaction uniquely well because of the ability of the pendant amine functionality – which cannot readily undergo hydrogen bonding due to the steric environment – to stabilise the electron-deficient gold-carbene and therefore promote its formation (Scheme **25**(b)).

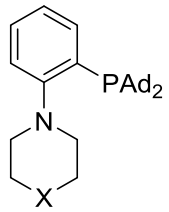
Scheme 26. Oxazole formation promoted by [Au(MorDalPhos)(NTf_2)]. Yields determined by ^{1}H NMR analysis *versus* an internal standard.



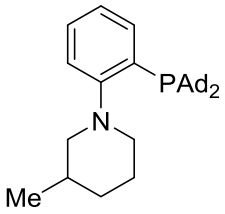
Ji *et al.* subsequently studied the related reaction involving carboxylic acids and alkynes to form ketoesters (Scheme 27).[72] This also proceeds through a gold-carbene/gold-stabilised carbenium intermediate. In this study, a wider range of amine-functionalised ligands were examined. In the model reaction of 1-dodecyne with benzoic acid, using 8-methylquinoline-*N*-oxide as the oxidant, triphenylphosphine (**P-1**), IPr (**NHC-1**), and BrettPhos (**P-45**) were ineffective (<7% yield). Mor-DalPhos (**P-48**) performed relatively well (68% yield), but further structural optimisation of the ligand increased the yield to 84% (using **P-90**). Further changes to the reaction conditions, adjusting the ratio of alkyne to carboxylic acid to 1.3 to 1, allowed the isolation of the product in 96% yield (98% yield from ^{1}H NMR integration).

Scheme 27. Ligand optimisation for the trapping of gold-carbene/gold-stabilised carbenium intermediates with carboxylic acids. Yields determined by ^{1}H NMR integration versus an internal standard.

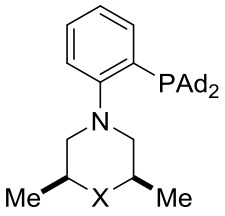




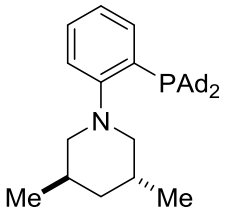
X = O **P-48** 68%
X = CH_2 **P-91** 68%
X = CH(Me) **P-92** 68%
X = CH(*t*-Bu) **P-93** 18%



P-94
75%



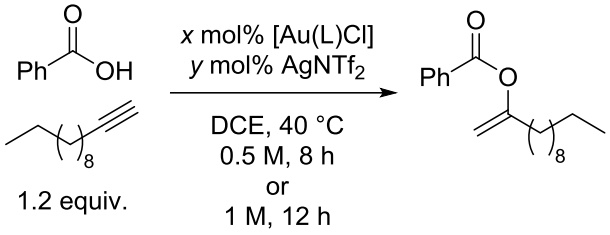
X = CH_2, R = Me **P-90** 84%
X = O, R = Me **P-96** 79%
X = O, R = Ph **P-97** 63%



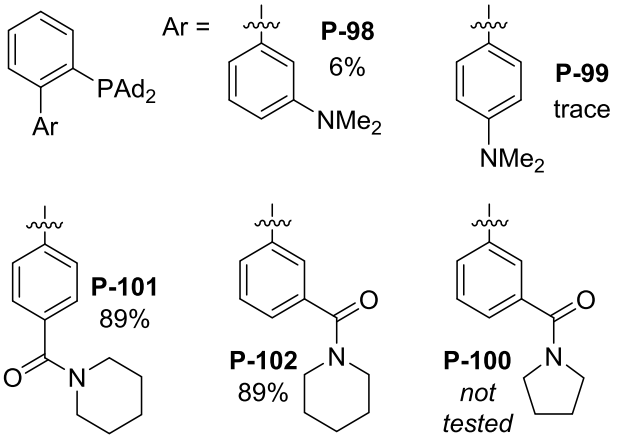
P-95
30%

Wang *et al.* designed a Buchwald-type ligand with an amide substituent that is proposed to direct nucleophiles when bound to a gold centre during catalysis;[73] this has been used for the branch-selective hydrocarboxylation of alkynes (Scheme 28). IPr (**NHC-1**), JohnPhos (**P-30**), and various regioisomers of AdDavePhos (**P-98** and **P-99**) are all ineffective for this reaction, while new ligand **P-100** was highly efficient, reaching turnover numbers in excess of 300,000 in some reactions (25 ppm [AuCl(**P-100**)], 0.12 mol% NaBAr$^{F}_{24}$ in fluorobenzene at 80 °C for 12 h). The hydrogen bonding reaction between the amide functionality within the ligand and the incoming nucleophile is proposed to be key to the efficacy of the resulting gold catalysts.

Scheme 28. Amide-functionalised ligands for gold-catalysed alkyne hydrofunctionalisation. Conversions were determined by ^{1}H NMR integration.



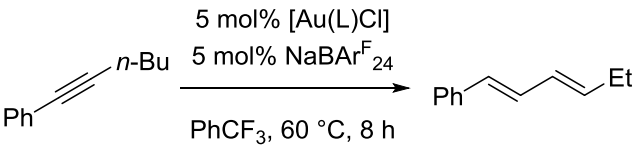
With 1.1 mol% [Au(L)Cl], 1 mol% $AgNTf_2$, 0.5 M, 8 h:

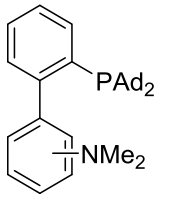


With 0.11 mol% [Au(L)Cl], 0.1 mol% $AgNTf_2$, 0.5 M, 8 h:	**P-101** 67%	**P-102** 91%
With 0.022 mol% [Au(L)Cl], 0.02 mol% $AgNTf_2$, 1 M, 12 h:	**P-100** 43%	**P-102** 37%

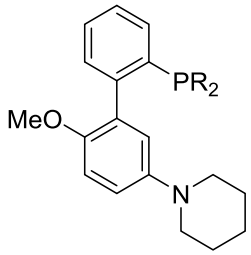
Wang deployed a similar suite of ligands in the gold-catalysed isomerisation of alkynes to 1,3-dienes (Scheme 29).[74] Performance in catalysis varied depending on the position of the basic group, with new ligand **P-103** giving 90% conversion, while other examples gave lower or no conversions. The basic group is proposed to interact with the propargylic proton and act as a proton shuttle during the reaction.

Scheme 29. Amine-functionalised ligands for gold-catalysed alkyne isomerisation. Conversions were determined by ^{1}H NMR integration using an internal standard.

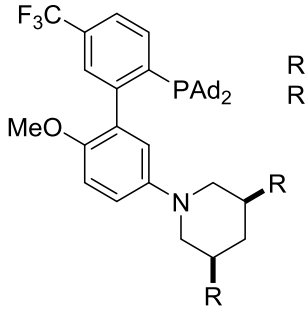




ortho **P-104** 3%
meta **P-98** 0%
para **P-99** 19%



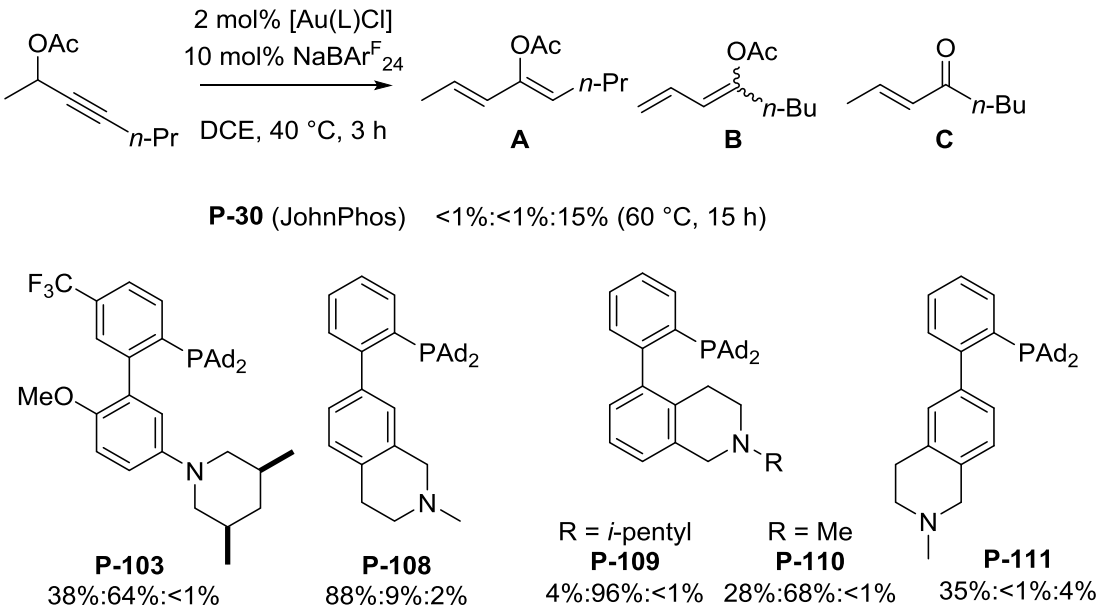
R = Ad **P-105** 35%
R = Cy **P-106** 4%



R = H **P-107** 77%
R = Me **P-103** 90%

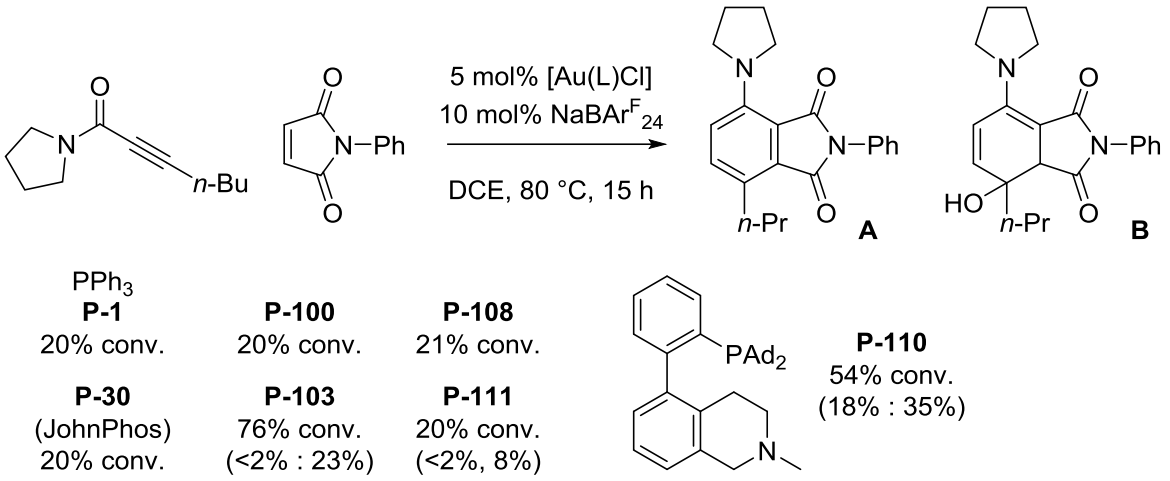
Wang *et al.* reported the divergent behaviour of different Buchwald-type phosphine ligands with basic amine groups in different positions when applied to the isomerisation reactions of propargylic esters (Scheme 30).[75] Ligand **P-108** leads selectively to product **A**, while ligand **P-109** gives product **B**. This is proposed to arise from deprotonation at different positions, the selectivity of which depends on the formation of the vinylgold intermediate. A JohnPhos-based catalyst gave only low yields of a side product (**C**). The reaction scope was studied using a range of propargylic acetate and pivalate substrates.

Scheme 30. Amine-functionalised ligands for gold-catalysed propargylic ester isomerisation. Conversions were determined by ^{1}H NMR integration using an internal standard.



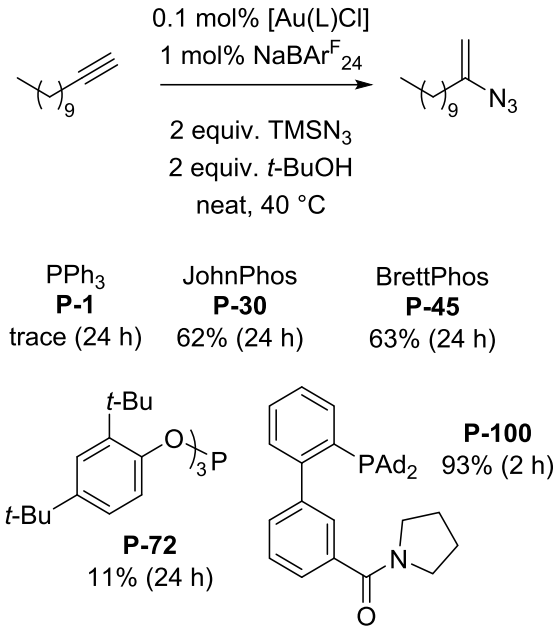
Li *et al.* have used similar Buchwald-type phosphine ligands to achieve the isomerisation of ynamides and allenamides to 1-amide-1,3-dienes;[76] these then undergo *in situ* Diels-Alder reactions to form heterocyclic scaffolds. In related work, Li and Ma *et al.* developed synthetic methodology for the cycloisomerisation of alkynamides to 2-aminofurans, which are then trapped by dienophiles to form the desired Diels-Alder adducts (Scheme 31).[77] The isomerisation step relied on a (biaryl)diadamantylphosphine ligand in which a tertiary amine was located in the correct position, which was proposed to be due to this acting as a 'proton shuttle'. Notably, several structurally very similar ligands were ineffective or poorly effective for the same transformation. Ligand **P-110** was taken forward in the reaction optimisation; longer reaction times (30 h) and the use of Boc_2O as an additive increased conversion to 100%, with 91% selectivity for product **A**, which was then isolated in 86% yield.

Scheme 31. Amine-functionalised ligands for gold-catalysed ynamide isomerisation/Diels-Alder reaction. Conversions were determined by ^{1}H NMR integration using an internal standard.



Li *et al.* used a catalyst with ligand **P-100** to enable the hydroazidation of alkynes in a regioselective fashion (Scheme 32).[78] The selectivity of the reaction was proposed to be due to hydrogen bonding interactions in the nucleophilic attack transition state. Alternative ligands without the amide functional group, such as JohnPhos (**P-30**) and BrettPhos (**P-45**), were found to be less effective, giving yields up to *ca.* 60% but at rather longer reaction times.

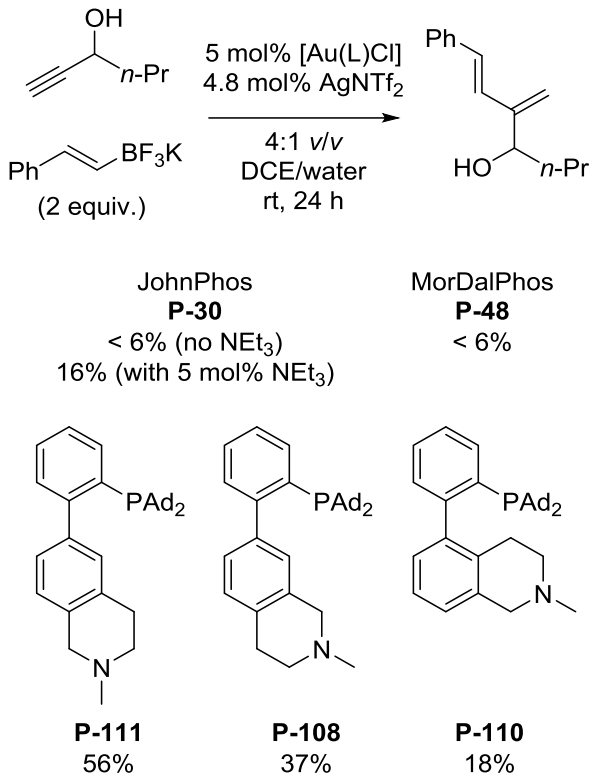
Scheme 32. Amide-functionalised ligands for gold-catalysed addition of azide to alkynes. Conversions were determined by ^{1}H NMR integration using an internal standard.



Liao *et al.* have applied designed Buchwald-type ligands with appended Lewis bases to the intermolecular addition of vinyl(trifluoro)borates to propargylic alcohols (Scheme 33).[79] The basic

group is proposed to undergo hydrogen bonding to the alcohol functional group, which in turn interacts with the Lewis acidic vinylB(F)(OH) species (formed by trifluoroborate hydrolysis); this mechanistic hypothesis is supported by DFT calculations. The reaction selectively forms the branched 1,3-diene product. If chiral alcohols are used, the reaction is stereoretentive. Alternative catalysts with triphenylphosphine (**P-1**), IPr (**NHC-1**), or JohnPhos (**P-30**) gave little or no product, while catalysts that have ligands with the basic group in other positions gave low yields (<40%). Reactions using [Au(**P-111**)Cl] were further optimised (to 77% conversion to product) by switching the solvent mixture to DCM/water and using three equivalents of the trifluoroborate reagent.

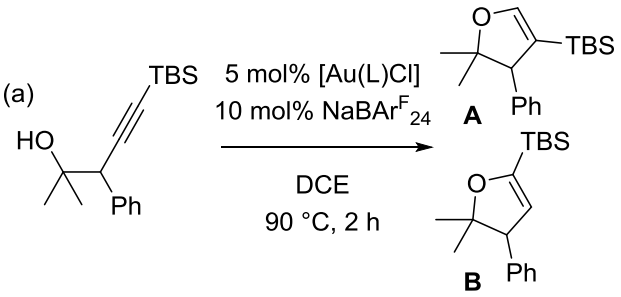
Scheme 33. Amine-functionalised ligands for gold-catalysed addition of vinylboron reagents to alkynes. Conversions were determined by ^{1}H NMR integration using an internal standard.



Li *et al.* have used (biaryl)di(adamantyl)phosphine ligands with a built-in 'proton shuttle' to achieve the cyclisation of homopropargylic alcohols to form dihydrofuran products (Scheme 34 (a)).[80,81] Catalysts with ligand **P-110** gave good conversions to product **A**, while the replacement of a methyl with a hydrogen (**P-112**) switched the selectivity to product **B**, albeit in moderate yield. Catalysts with ligands without basic functionality performed poorly, and once again an amino group was needed in the correct position to achieve the best results. DFT calculations support the involvement of this bifunctional ligand in hydrogen bonding to the alcohol during the cyclisation step.

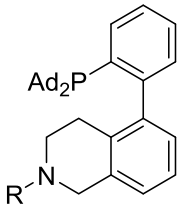
It was also possible to achieve the one-pot reaction of aryl aldehydes with benzyl silylacetylenes to form dihydrofurans without the detection of the intermediate propargylic alcohol (Scheme 34 (b)).

Scheme 34. (a) Cyclisation of propargylamines. (b) One pot dihydrofuran synthesis from aryl aldehydes and benzyl silylacetylenes. Conversions were determined by ^{1}H NMR integration using an internal standard.

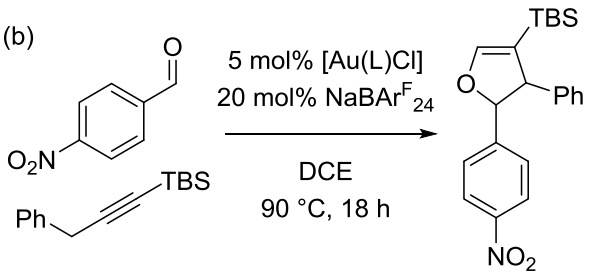


JohnPhos 0% (no NEt_3)
P-30 15% (0:1) (10 mol% NEt_3)

P-108 <5%
P-111 <5%

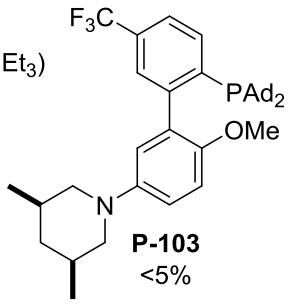


R = Me **P-110** 92% (>50:1)
R = H **P-112** 55% (<1:10)
R = *iso*-pentyl **P-109** 20% (>50:1)



JohnPhos 0% (no NEt_3)
P-30 <5% (10 mol% NEt_3)

P-108 <5%
P-111 <5%
P-110 78%
P-109 15%



P-103
<5%

While a diverse range of reactions has been achieved using gold catalysts with ligands that possess basic amine functionality, the placement of the basic group in each case is crucial to achieving good yields and the desired selectivity. Much of this work is also supported by DFT calculations, and

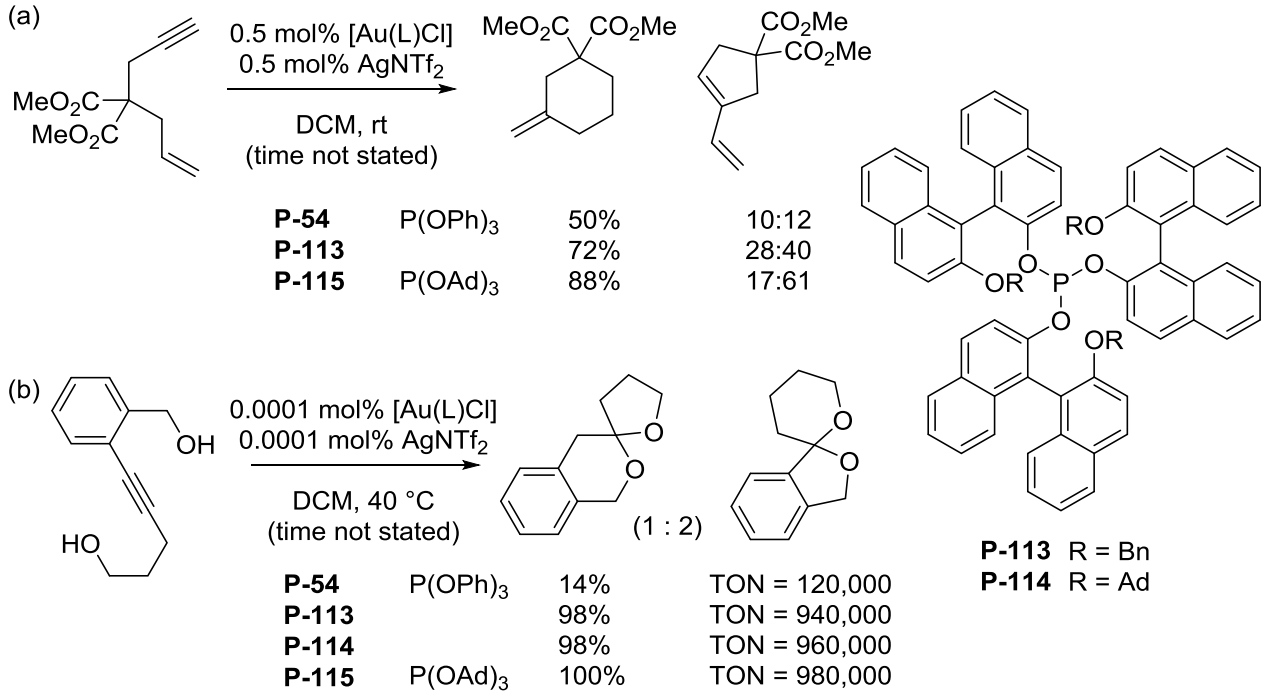
so in principle future ligand and reaction design in this area could potentially be guided by such calculations.

2.8 Phosphites

Phosphites are phosphorus-based ligands that tend to be less electron-rich than their phosphine counterparts due to their increased π-accepting character.[11] This should render the corresponding gold complexes more electrophilic, and could therefore accelerate catalytic reactions where the nucleophilic attack step is rate-determining,[9] in much the same way as is proposed for the other classes of electron-poor ligand discussed previously.

Blanco Jaimes *et al.* have designed a series of sterically very large phosphite ligands for gold catalysis and compared these to triphenyl phosphite (**P-54**) in some model reactions (Scheme 35).[82] Ligands include highly bulky BINAP-derived **P-113** and **P-114**, and triadamantylphosphite (**P-115**). These gave better yields and selectivities than triphenylphosphite (**P-54**) in the cycloisomerisation of 1,6-enynes and performed well in the Hashmi phenol synthesis (up to 88% yield at 0.1 mol% catalyst loading). For spirocyclisation reactions, the new ligands offered comparable performance to triphenylphosphite at loadings as low as 0.01 mol%, but significantly outperformed triphenylphosphite at lower catalyst loadings; this was proposed to be due to the stabilisation of the gold species by the very bulky *P*-substituents, preventing (or decreasing the rate of) catalyst decomposition.

Scheme 35. Comparison of phosphite ligands in gold catalysis.

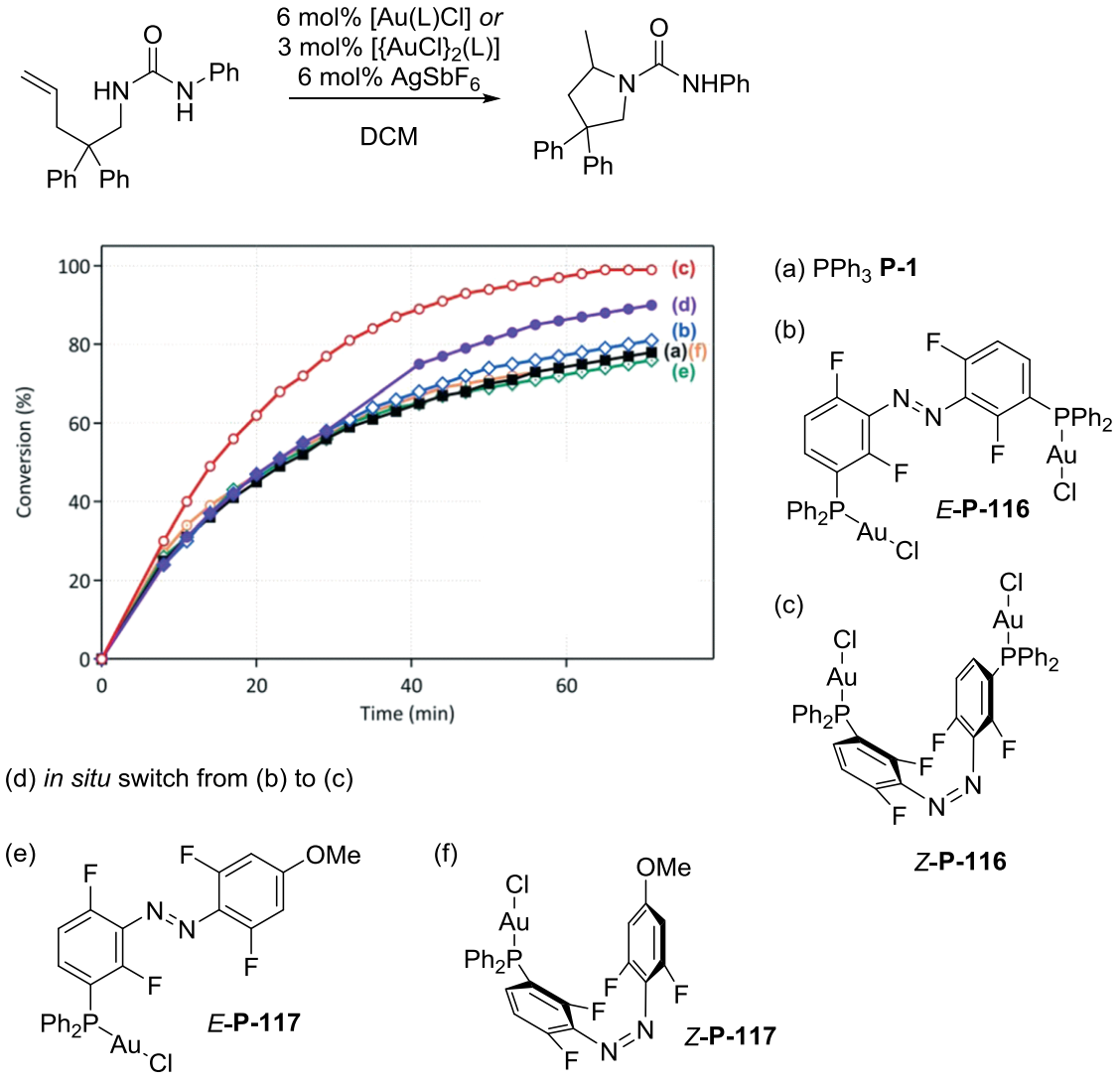


2.9 Switchable Phosphorus Ligands

Switchable ligands can be broadly defined as ligands that change structure and/or properties based on a response to an external stimulus, such as light or heat.[83] These can then potentially be used to switch catalysis on or off, or switch reaction selectivity, for example.

Arif *et al.* have synthesised phosphine ligands **P-116** and **P-117** based on a photoswitchable azobenzene framework (Scheme 36).[84] Ligand **P-116** was originally prepared in the *E*-configuration, but irradiation with 320 nm light causes the ligand to switch to the *Z*-configuration. Heating or irradiation with 406 nm light can then switch the ligand back to the *E*-configuration. This ligand was compared to PPh_3 in two model reactions. In the intramolecular hydroamination of a urea substrate, a rate difference between reactions catalysed by gold complexes with the *E*- and *Z*-isomers of the ligand was observed, with the latter leading to a faster reaction. The catalyst with the *E*-isomer gave comparable results to [Au(PPh_3)Cl], but irradiation with 320 nm light part-way through the reaction triggered a significant rate increase. These data were used to suggest that both gold centres were involved in the cyclisation reaction, perhaps in the form of bimetallic activation of the substrate. In contrast, no difference in reactivity was observed for the cyclisation of an enyne substrate: [Au(PPh_3)Cl] and the complexes derived from the *E*- and *Z*-isomers of the photoswitchable ligand gave essentially identical conversion/time profiles.

Scheme 36. Diphosphene ligands for gold-catalysed intramolecular hydroarylation reactions. Graph modified from reference [84].



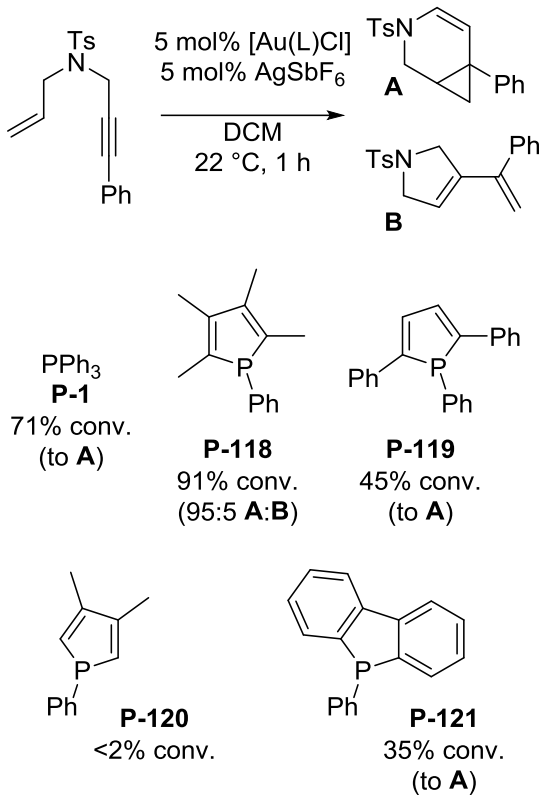
2.10 Other Phosphorus Ligands

As well as the more established ligands, other phosphorus-based ligands have been applied in gold catalysis. These are collected in this section for completeness.

Fourmy *et al.* have tested phosphole ligands in gold catalysis.[85] Four examples (**P-118** – **P-121**) were examined and compared to triphenylphosphine in the cycloisomerisation of 1,6-enynes (Scheme 37). These ligands underwent catalytic turnover with varying degrees of efficiency; 2,3,4,5-tetramethylphosphole (**P-118**) gave the best performance, exceeding that of triphenylphosphine (**P-1**). In the cyclopropanation of styrenes and norbornene, which triphenylphosphine-bearing catalysts do not successfully catalyse, the phosphole-derived ligands gave yields of 14 – 99%, with 2,3,4,5-tetramethylphosphole (**P-118**) again appearing to be the most promising. This ligand was found to be

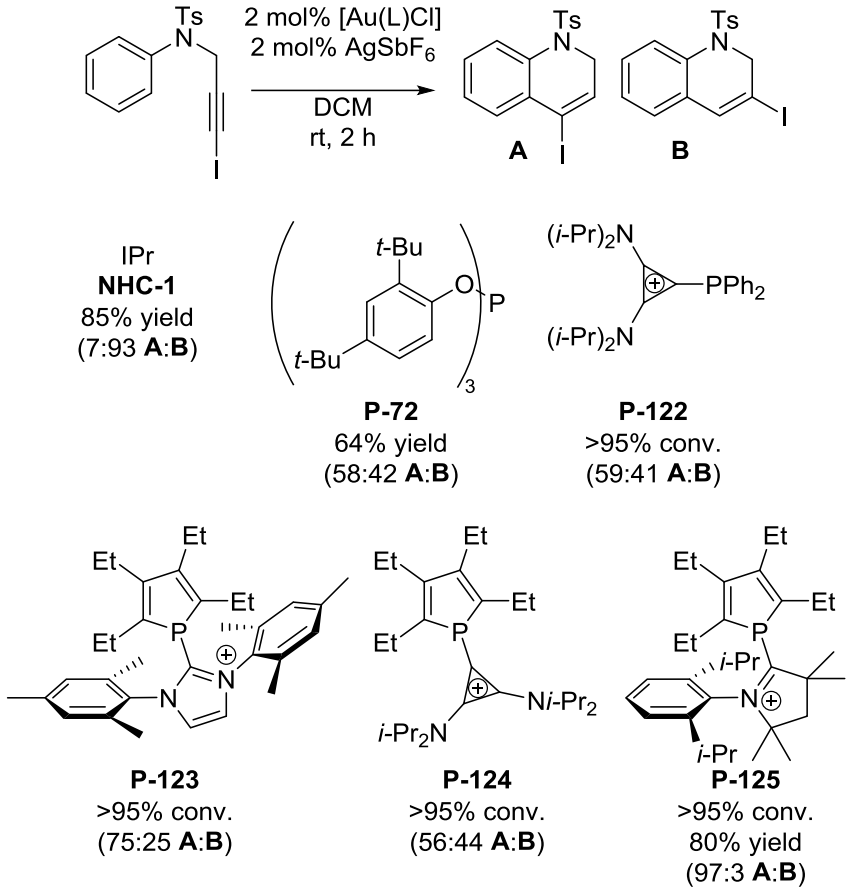
the most electron-donating, as determined by quantifying TEP using the corresponding $[RhCl(CO)_2(L)]$ complexes.

Scheme 37. Phospholes as ligands for gold-catalysed enyne cyclisation reactions.



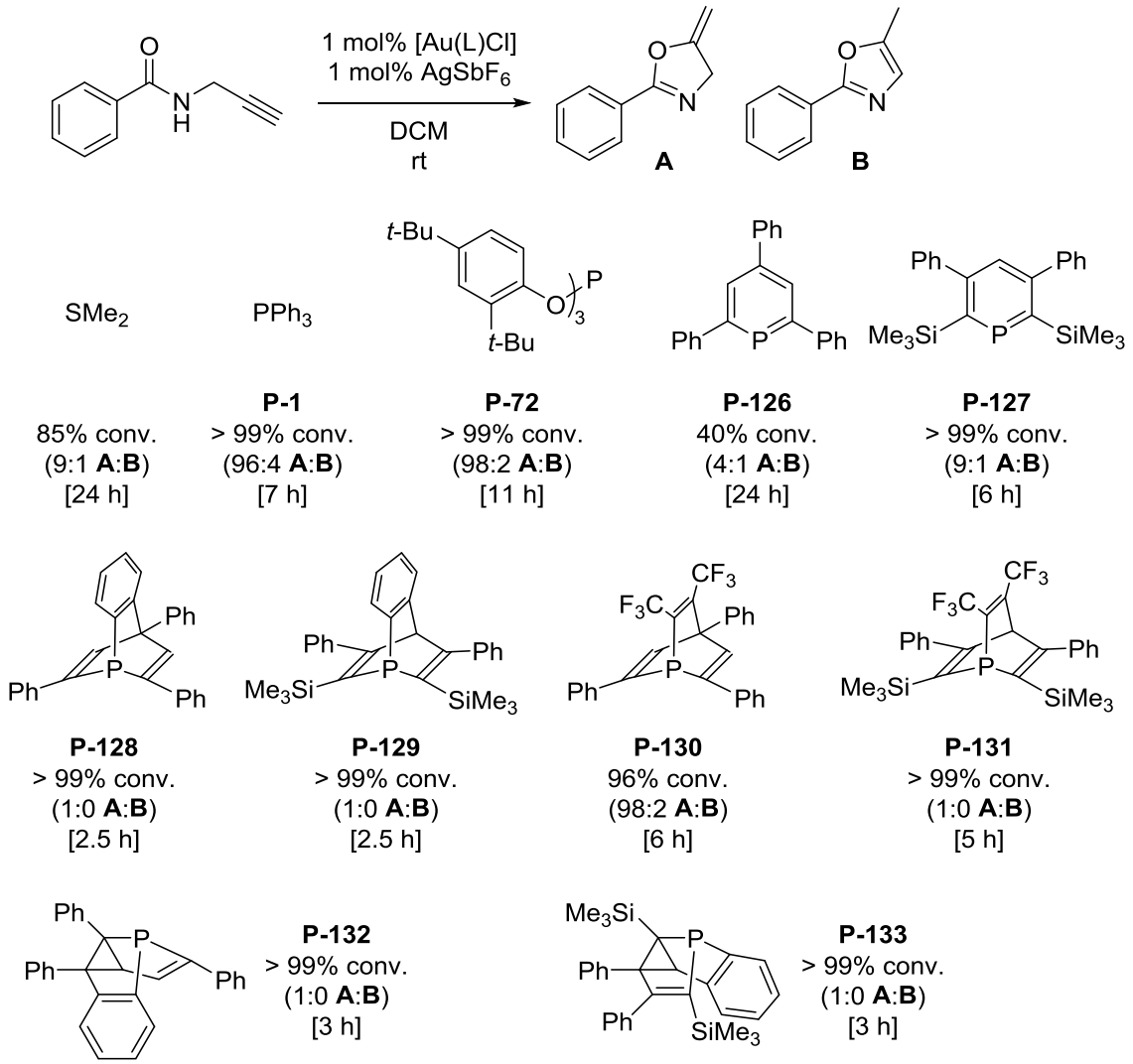
More recently, Johannsen *et al.* compared an α-cationic phosphine (**P-122**) to a series of α-cationic phospholes (**P-123** – **P-125**) and applied these in gold catalysis;[86] this combines the electron deficient nature of α-cationic phosphines with the enhanced π-accepting properties of phospholes (compared to phosphines). IR analysis of $[RhCl(CO)(L)_2]$ complexes confirmed that one of these new α-cationic phospholes (**P-124**, with a cyclopropylium *P*-substituent) were indeed less electron rich than the corresponding cyclopropylium-substituted diphenylphosphine (**P-122**) ($\Delta\nu_{CO}$ = 13 cm^{-1}). The corresponding gold complexes were shown to be effective for challenging alkyne hydroarylation reactions, outperforming α-cationic phosphines, phosphites, and IPr (Scheme 39).

Scheme 38. Use of α-cationic phospholes in gold catalysis.



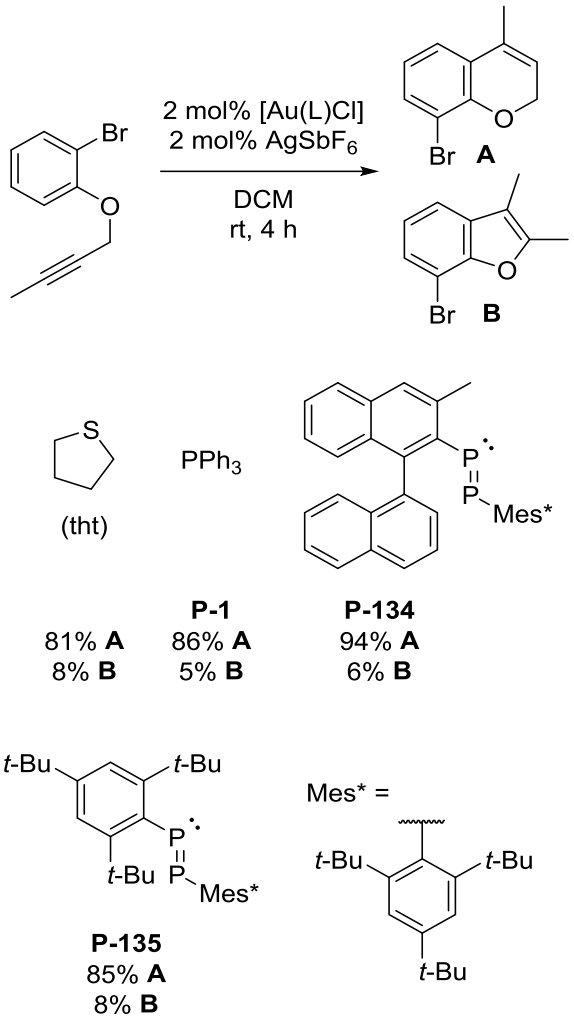
Rigo *et al.* prepared a series of phosphinine-based ligands (**P-126** – **P-133**) and evaluated their structural parameters and catalytic performance (Scheme 39).[87] These ligands included substituted phosphinines, phosphabarrelenes, and phosphasemibullvalenes, which all have rather different σ- and π-bonding properties compared to trialkylphosphines or triarylphosphines, with less pronounced σ-character compared to triphenylphosphine (**P-1**). The corresponding gold complexes ([Au(L)Cl] plus $AgSbF_6$) were assessed for the intramolecular cyclisation reactions of *N*-propargylbenzamide; several examples offered improved catalytic performance compared to [Au(PPh_3)Cl].

Scheme 39. Phosphinines ligands for gold-catalysed propargylamide cyclisation reactions.



Tsurusaki *et al.* have prepared 1,1-binapthyldiphosphene ligands (**P-134** and **P-135**) and applied them to gold-catalysed hydroarylation reactions (Scheme 40).[88] Ligand **P-134** coordinates the gold centre at the phosphorous atom closest to the binapthyl fragment, due to the bulky Mes* (2,4,6-tri(*tert*-butyl)phenyl) substituent on the other phosphorous atom. The corresponding gold catalyst was found to yield similar results in catalysis to [Au(tht)Cl] and [Au(PPh_3)Cl]; attempts to achieve atroposelective hydroarylation using a suitable substituted substrate led to very low *ee*s (<10%).

Scheme 40. Diphosphene ligands for gold-catalysed intramolecular hydroarylation reactions.



3 *N*-Heterocyclic Carbene Ligands

N-heterocyclic carbenes (NHC) have become an outstanding ligand class in gold-catalysed transformations.[89-92] In this section, the development of NHC ligands and their impact in gold catalysis will be discussed. The NHC ligands are organised by core structure, including subsections for structural modifications (Figure 4). Chiral-NHCs are not discussed.[35] It should be noted that some of the NHC ligands described might fit in more than one classification and have been placed in the more relevant section. Additionally, it should be noted that not all of the carbenes have been isolated as "free carbenes". Only the protocols where the new ligands have been benchmarked *versus* common ligands are described.

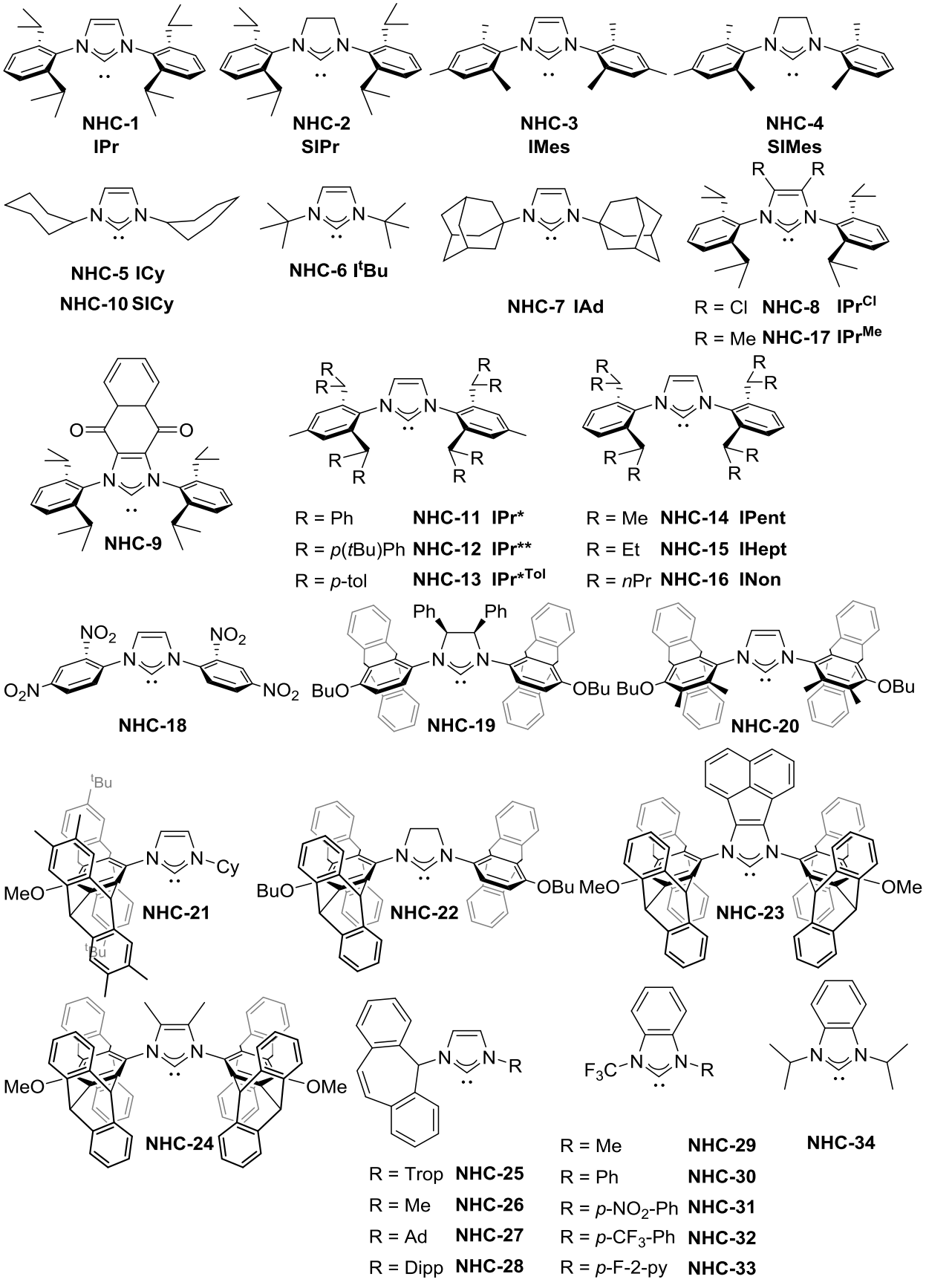


Figure 4. NHC-structures discussed in this review.

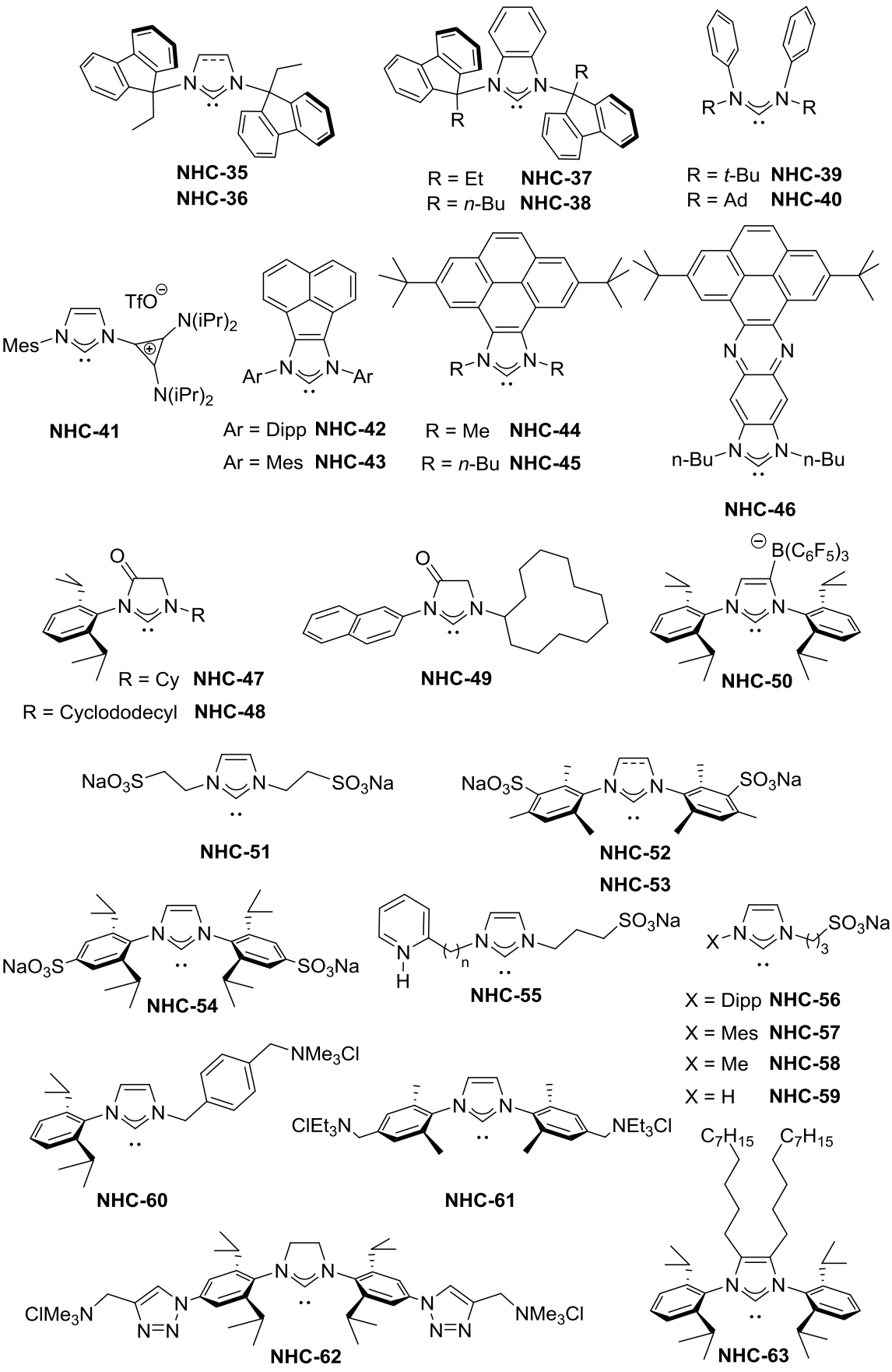
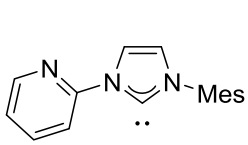
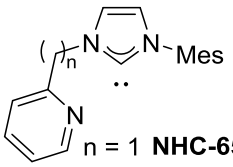


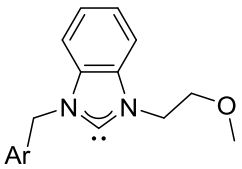
Figure 4 (continued). NHC-structures discussed in this review.



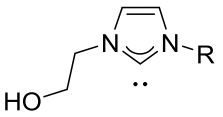
NHC-64



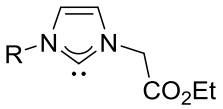
n = 1 **NHC-65**
n = 2 **NHC-66**



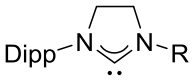
Ar = Ph **NHC-67**
Ar = 2-py **NHC-68**



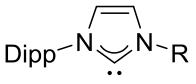
R = Dipp **NHC-69**
R = Mes **NHC-70**
R = Me **NHC-71**



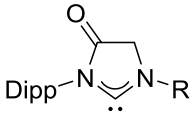
R = CH_2CO_2Et **NHC-72**
R = Me **NHC-73**
R = Mes **NHC-74**
R = Dipp **NHC-75**



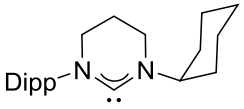
R = Cy **NHC-76**
R = cyclooctyl **NHC-77**
R = cyclododecyl **NHC-78**
R = cyclopentadecyl **NHC-79**



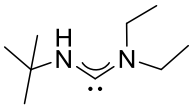
R = Cy **NHC-80**
R = cyclooctyl **NHC-81**
R = cyclododecyl **NHC-82**
R = cyclopentadecyl **NHC-83**



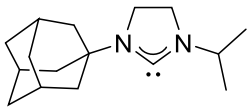
R = Cy **NHC-84**
R = cyclooctyl **NHC-85**
R = cyclododecyl **NHC-86**
R = cyclopentadecyl **NHC-87**



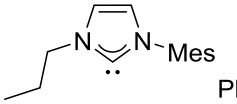
NHC-88



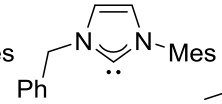
NHC-89



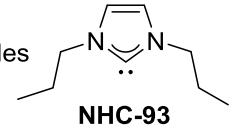
NHC-90



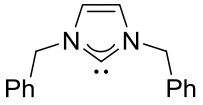
NHC-91



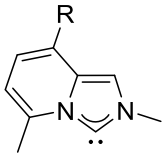
NHC-92



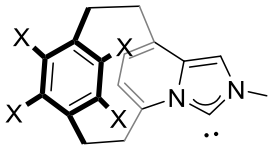
NHC-93



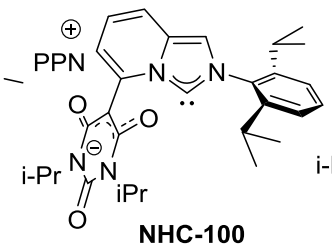
NHC-94



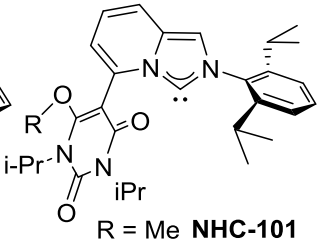
R = H **NHC-95**
R = Me **NHC-96**



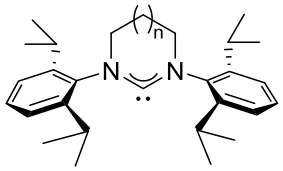
X = H **NHC-97**
X = F **NHC-98**
X = OMe **NHC-99**



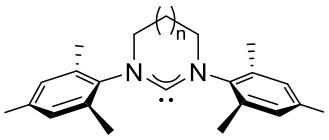
NHC-100



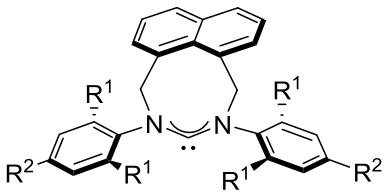
R = Me **NHC-101**
R = Tf **NHC-102**



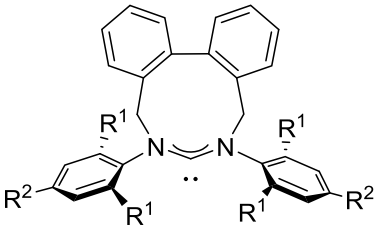
n = 1 **NHC-103**
n = 2 **NHC-104**



n = 1 **NHC-105**
n = 2 **NHC-106**
n = 3 **NHC-107**

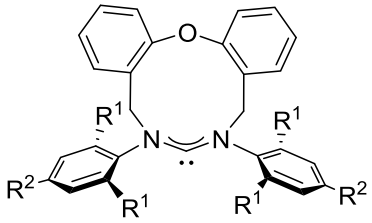


R^1 = *i*-Pr; R^2 = H **NHC-108**
R^1 = Me; R^2 = H **NHC-109**
R^1 = Me; R^2 = Me **NHC-110**

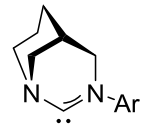


R^1 = Me; R^2 = Me **NHC-111**
R^1 = *i*-Pr; R^2 = H **NHC-112**
R^1 = Me; R^2 = H **NHC-113**
R^1 = Et; R^2 = H **NHC-114**

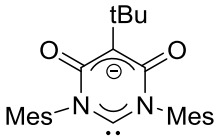
Figure 4 (continued). NHC-structures discussed in this review.



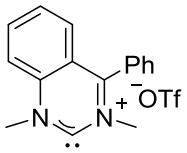
R^1 = Me; R^2 = Me **NHC-115**
R^1 = *i*-Pr; R^2 = H **NHC-116**
R^1 = Me; R^2 = H **NHC-117**
R^1 = Et; R^2 = H **NHC-118**



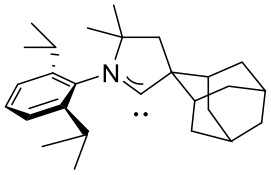
Ar = Dipp **NHC-119**
Ar = Mes **NHC-120**
Ar = Ph **NHC-121**
Ar = Tol **NHC-122**
Ar = *p*-NO_2-Ph **NHC-123**
Ar = -SO_2-tol **NHC-124**



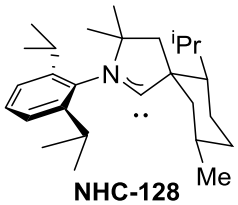
NHC-125



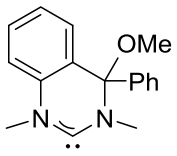
NHC-126



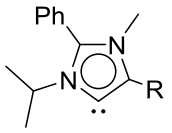
NHC-127



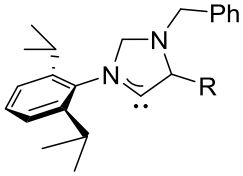
NHC-128



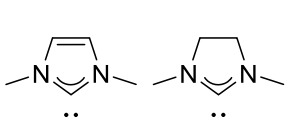
NHC-129



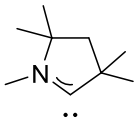
R = Ph **NHC-130**
R = *i*-Pr **NHC-131**



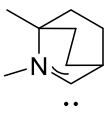
R = Me **NHC-132**
R = H **NHC-133**



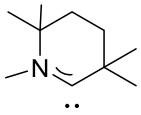
IMe **NHC-134**
SIMe **NHC-135**



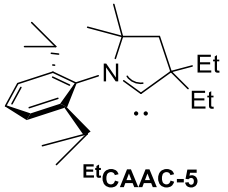
CAAC-5 **NHC-136**



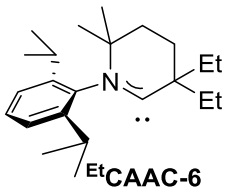
BiCAAC **NHC-137**



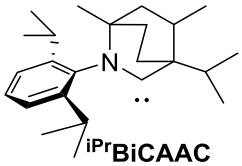
CAAC-6 **NHC-138**



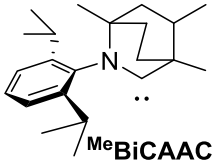
^{Et}**CAAC-5** **NHC-139**



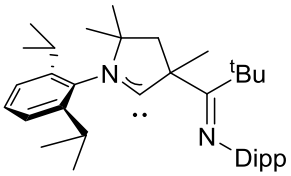
^{Et}**CAAC-6** **NHC-140**



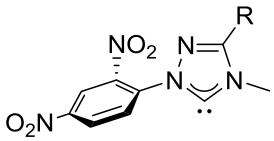
^{iPr}**BiCAAC** **NHC-141**



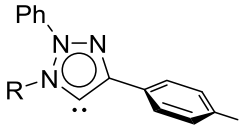
^{Me}**BiCAAC** **NHC-142**



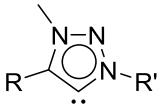
NHC-143



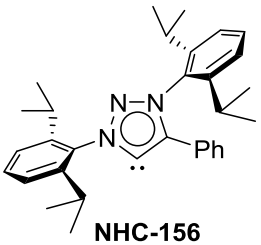
R = H **NHC-144**
R = NO_2 **NHC-145**



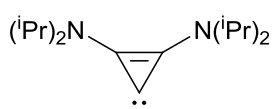
R = CH_3 **NHC-146**
R = Cy **NHC-147**



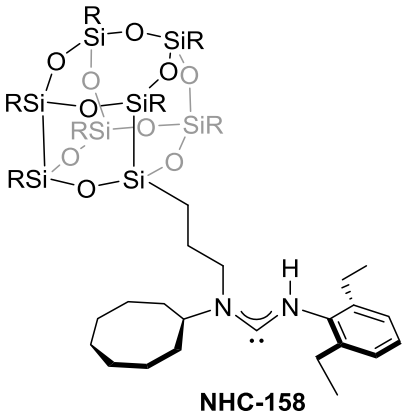
	R	R'
NHC-148	Ph	Bn
NHC-149	*p*-OMePh	Bn
NHC-150	*p*-NO_2Ph	Bn
NHC-151	Bn	Bn
NHC-152	Ph	Ph
NHC-153	Mes	Mes
NHC-154	Bn	$CHCH_3Ph$
NHC-155	-(S=O)Ph	$CHCH_3Ph$



NHC-156



NHC-157



NHC-158
R= ^{i}Bu

Figure 4 (continued). NHC-structures discussed in this review.

3.1 Imidazolin-2-ylidenes, imidazolidin-2-ylidenes and related structures

Imidazolin-2-ylidenes and their backbone saturated analogues are the most studied NHCs. Some of the most common examples, and the ones used in initial studies about Au-NHC catalysis, are those shown in Figure 5 (**NHC 1**-**7**).[90,91]

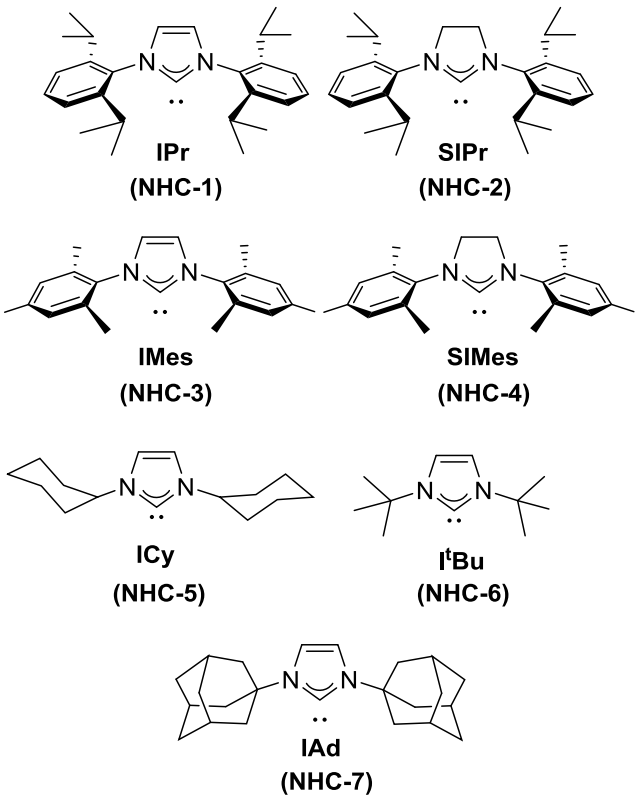


Figure 5. Most commonly employed imidazolin-2-ylidenes and imidazolidin-2-ylidenes ligands

Amongst these ligands, IPr (**NHC-1**) is by far the most common NHC ligand in homogeneous gold catalysis. The reasons for that are likely a combination of factors, [Au(IPr)Cl], IPr and IPr·HCl are commercially available and their syntheses are straightforward.[93-99] IPr is a strongly donating ligand TEP (2051.5 cm^{-1})[100] with a high steric volume (%V_{bur} 45.4)[30] which stabilises the [Au-IPr]$^+$ fragment. [Au(IPr)Cl], in combination with a halide abstractor, is usually the first choice when it comes to Au-NHC catalysed processes and, in general, shows good catalytic activity, being still used in many transformations. IPr is also used as a benchmark ligand to evaluate the influence of new NHC ligands in metal catalysis. In this section, we will focus on NHC modifications that have been explored in the literature and highlight the ligand effect on gold catalysis.

Initially, direct modifications of the IPr structure (tuning of the backbone and steric hindrance) will be presented. Then, the development of other imidazol(id)in-2-ylidene ligands for gold catalysis will be discussed, grouped according to their structural features. Only those carbenes that have been employed as ligands in gold catalysis and benchmarked against common NHCs are included.

3.1.1 Common modifications of 'IPr'

3.1.1.1 Backbone modification.

NHC backbone modification is a useful strategy to mainly tune the electronic properties of carbene ligands.[13] In this section, IPr backbone saturation (SIPr, **NHC-2**) and substitution (IPr^{Cl}, **NHC-8**) will be discussed (Figure 6).

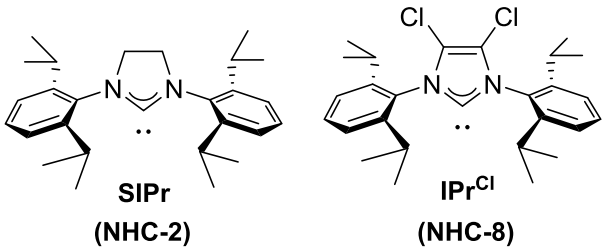


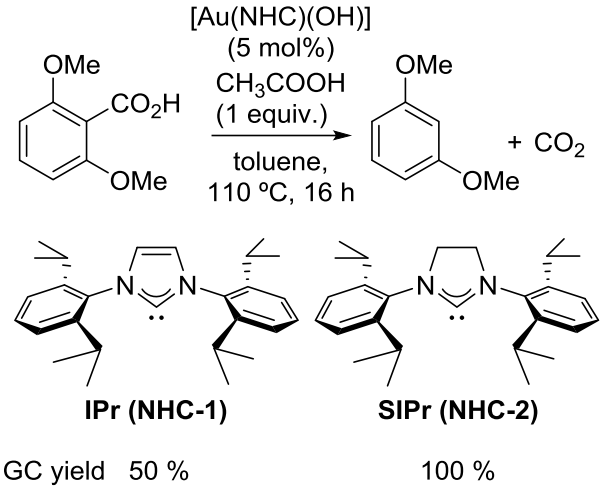
Figure 6. IPr-backbone modifications

SIPr (**NHC-2**) is the saturated analogue of IPr (**NHC-1**). Backbone saturation modifies the electronic and steric properties of the carbene. SIPr is more σ-donating than IPr, but also more π-accepting, which results in a lower net electron-donating ability (TEP = 2052.2 cm^{-1} for SIPr *versus* 2051.5 cm^{-1} for IPr).[12,13,21] SIPr is also bulkier than IPr (%V_{bur} : SIPr = 47.0; IPr = 45.4).[30]

SIPr is a common candidate in ligand screening for gold-catalysis. Usually, Au-SIPr complexes show similar or lower catalytic activity than Au-IPr complexes, and in most cases, the IPr derivative is preferred.[101] However, there are some reports where Au-SIPr derivatives have proven to be more efficient than Au-IPr species.

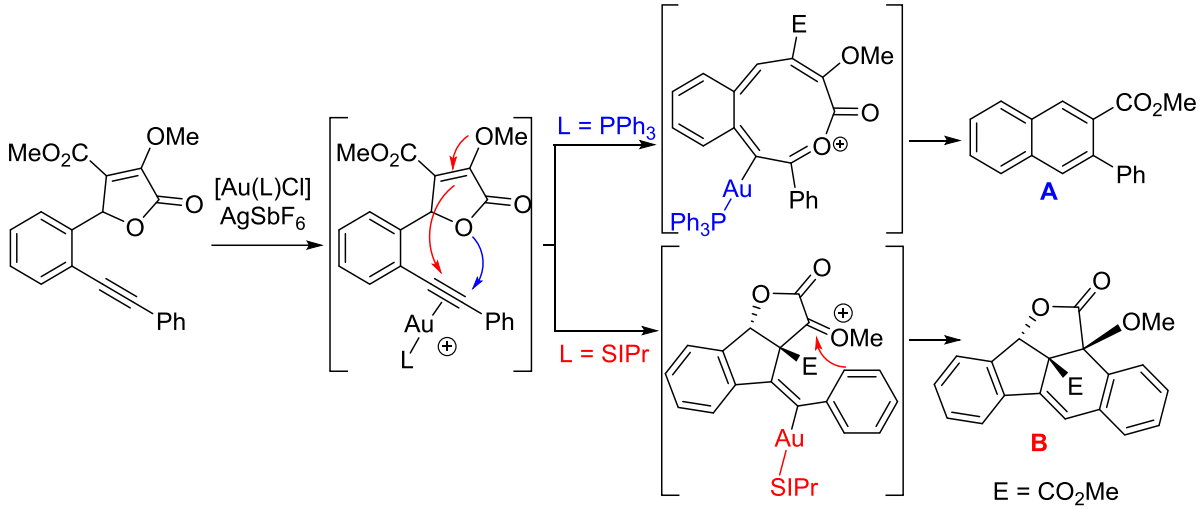
[Au(SIPr)(OH)] was found to be a more efficient catalyst than [Au(IPr)(OH)] for the protodecarboxylation of aromatic carboxylic acids in the presence of acetic acid.[102,103] Under the same conditions, [Au(SIPr)(OH)] gave full conversion of 2,6-dimethoxybenzoic acid to 1,3-dimethoxybenzene and CO_2; 50% conversion was obtained with [Au(IPr)(OH)]). The different reactivity was attributed to SIPr being a better π-accepting ligand than IPr, promoting a faster decarboxylation of the Au-carboxylate intermediate (Scheme 41).[102,103]

Scheme 41. Au-SIPr catalysed protodecarboxylation of aromatic carboxylic acids.



Chen, Zhu and co-workers showed that gold complexes can selectively promote the transformation of enyne-lactones into different compounds depending on the nature of the ligand employed.[104] When PPh_3 (**P-1**) was used as ligand, naphthalene derivatives were selectively obtained (product **A**, Scheme 42); using SIPr (**NHC-2**), however, the formation of benzo-fused polycyclic compounds (product **B**, Scheme 42) was favoured over the formation of product **A** (70 vs 13% isolated yield **B:A,** Scheme 42). Product **B** was proposed to form *via* a 5-exo-dig cyclisation and an intramolecular Friedel-Crafts reaction mechanism. Ligand screening showed that gold complexes containing IMes (**NHC-3**) and SIMes (**NHC-4**) did not promote any transformation, and Au-IPr systems (**NHC-1**) afforded mixtures of the two products.[104] In view of the results, a combination of factors is likely to determine the regioselectivity of the process. The stronger σ-properties of SIPr, compared to PPh_3, were suggested to favour the vinyl ether addition. However, IPr, being a more donating ligand than IPr lead to mixture of A and B.

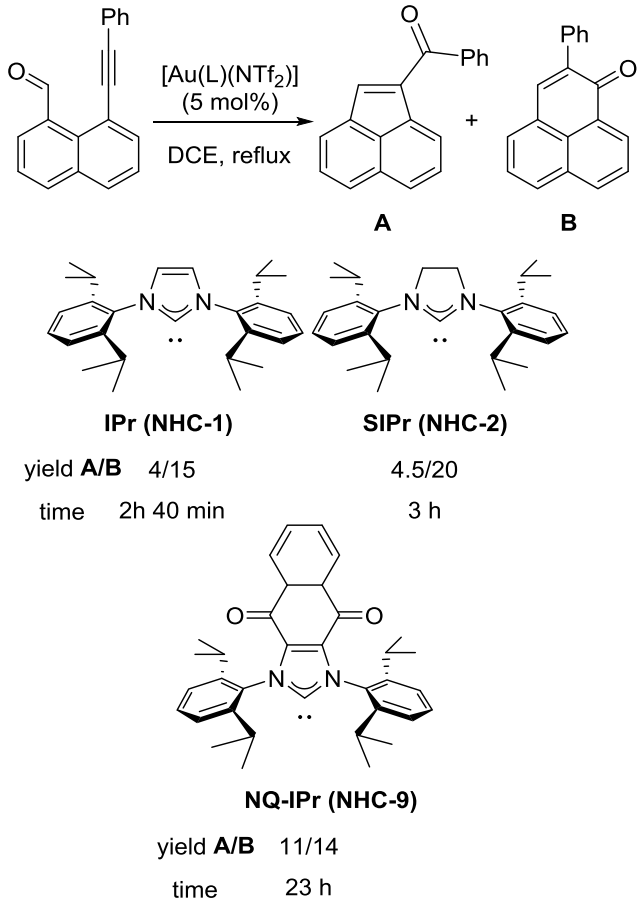
Scheme 42. Ligand effect in the gold-catalysed reaction of enyne-lactones (E = CO_2Me).



The chemoselectivity was proposed to be due to the electronic differences between SIPr (**NHC-2**) and PPh_3 (**P-1**). The authors suggested that the stronger donor properties of SIPr (**NHC-2**) would lead to the formation of a less electron-deficient alkyne species upon Au(SIPr)- coordination, favouring the vinyl ether addition (Scheme 42).[104]

SIPr (**NHC-2**) was also found to be superior to other ligands in the gold-promoted cyclisation of acenaphthaldehyde. Using PPh_3 (**P-1**) as the ligand, a complex mixture of species was obtained. Amongst the NHC ligands tested (IPr, **NHC-1**; SIPr, **NHC-2**; and NQ-IPr, **NHC-9**), all in the form of [Au(NHC)(NTf_2)] complexes, SIPr showed a higher selectivity towards species **B** (Scheme 43). The reaction was further optimised in the presence of various alcohols to obtain 3-alkoxy-benzo[de]isochromene derivatives.[105]

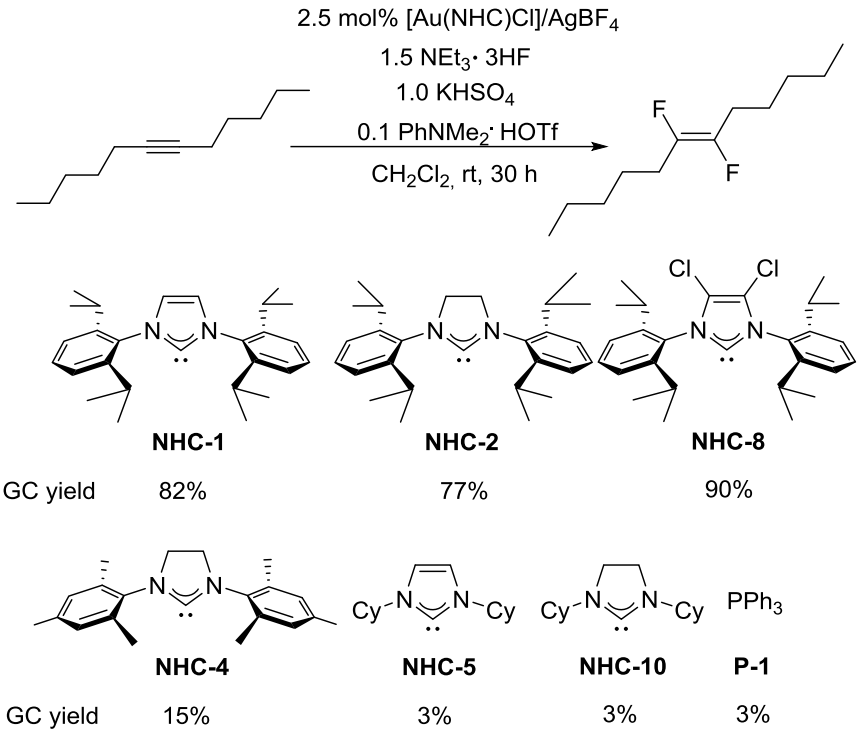
Scheme 43. Gold-catalysed cyclisation of acenaphthaldehyde



IPr^{Cl} (**NHC-8**), with Cl atoms in the backbone, shows a very similar %V_{bur} to that of IPr (44.9[30,106] vs 45.4[30]); however, as expected due to the electron withdrawing effect of the Cl atoms, IPr^{Cl} (**NHC-8**) is less electron-donating than IPr (TEP = 2055.1 vs 2051.5 cm^{-1}, respectively).[21] This modification has proven to be beneficial for a handful of catalytic transformations.

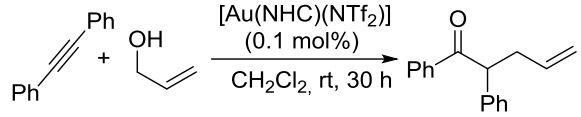
Sadighi and co-workers reported the Au-catalysed hydrofluorination of alkynes using $NEt_3 \cdot 3HF$ as a fluorinating agent.[107] Optimisation of the catalyst system [Au(L)Cl]/$AgBF_4$ showed that IPr based NHC ligands (IPr, **NHC-1**; SIPr, **NHC-2**; IPr^{Cl}, **NHC-8**) performed better than SIMes (**NHC-4**), ICy (**NHC-5**), SICy (**NHC-10**), or PPh_3 which all afforded very low yields. Amongst the three IPr-based species, the less electron-rich carbene IPr^{Cl} gave the higher reaction yield (Scheme 44). A later study on similar systems showed that increasing the steric bulk of the IPr ligand afforded better results for this transformation (see section 3.1.1.2).[108] These results might suggest a rate-limiting electronic activation process.

Scheme 44. Ligand effect in the hydrofluorination of alkynes.

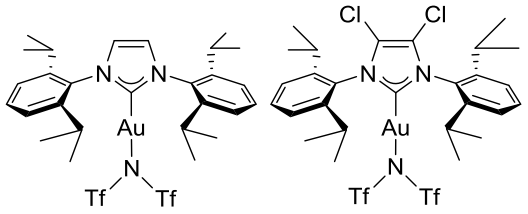


Homoallylic ketones were prepared via a sequential hydroalkoxylation of alkynes/Claisen rearrangement using Au-NHC catalysts.[109] Reactions were run at low catalyst loading and stopped after short reaction times to explore the ligand influence. The well-defined [Au(NHC)(NTf_2)] system bearing IPr^{Cl} (**NHC-8**) afforded higher yields than the IPr (**NHC-1**) and SIPr (**NHC-2**) complexes, and slightly higher yields than the bulky IPr* (**NHC-11**) derivative (Scheme 45).[109]

Scheme 45. Gold-catalysed hydroalkoxylation/Claisen rearrangement of allylic alochols and alkynes.

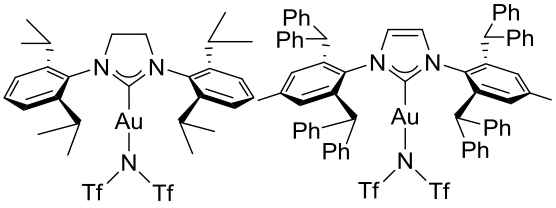


1 equiv. 3 equiv.



NHC-1 **NHC-8**

GC yield		
30 min	34%	40%
1 h	35%	50%



NHC-2 **NHC-11**

GC yield		
30 min	17%	41%
1 h	23%	46%

$[Au(IPr^{Cl})(NCCH_3)]BF_4$ is a highly efficient catalyst for the addition of aliphatic alcohols to internal alkynes[110] and in the dehydrative formation of ethers from benzylic alcohols and phenols.[111] In both transformations, the Au-IPr^{Cl} complex was found to be more efficient than the Au-IPr analogue.

3.1.1.2 Increased steric bulk

The steric bulk around IPr has been increased by modifying the isopropyl groups (Figure 7); these modifications include the incorporation of aromatic substituents (IPr*, **NHC-11**; IPr**, **NHC-12**; IPr^{*tol}, **NHC-13**), or longer alkyl chains (IPent, **NHC-14**; IHept, **NHC-15**; INon, **NHC-16**). The latter series are often referred to as 'ITent' ligands.

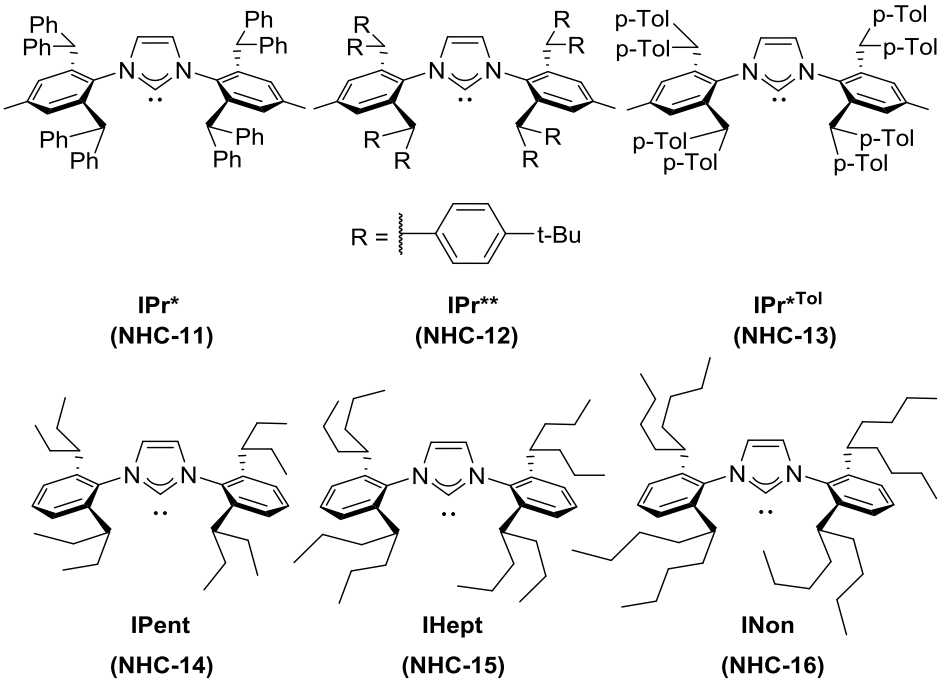
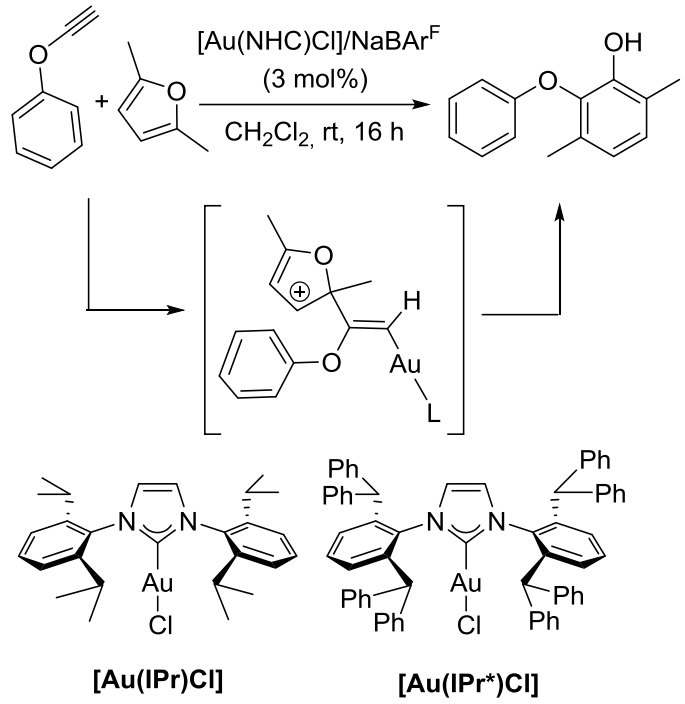


Figure 7. IPr-derivatives with increased steric bulk.

IPr* (**NHC-11**) is more sterically demanding than IPr (**NHC-1**) (%V_{bur} 50.4 vs 45.4),[30,112] and slightly less electron-donating (TEP 2052.1 vs 2051.5 cm^{-1})[100,113]. Therefore, the different reactivity of catalysts containing these two ligands has been attributed to steric factors.[114] IPr* has been compared to IPr and other NHCs in a number of transformations, such as allylic acetate rearrangement or the isomerisation of propargylic acetates into enones and indenes. Although catalytically active, gold complexes containing IPr* were slightly less active than Au-IPr derivatives.[112] However, there are some examples where IPr* has proven to be more efficient than IPr in gold catalysis.

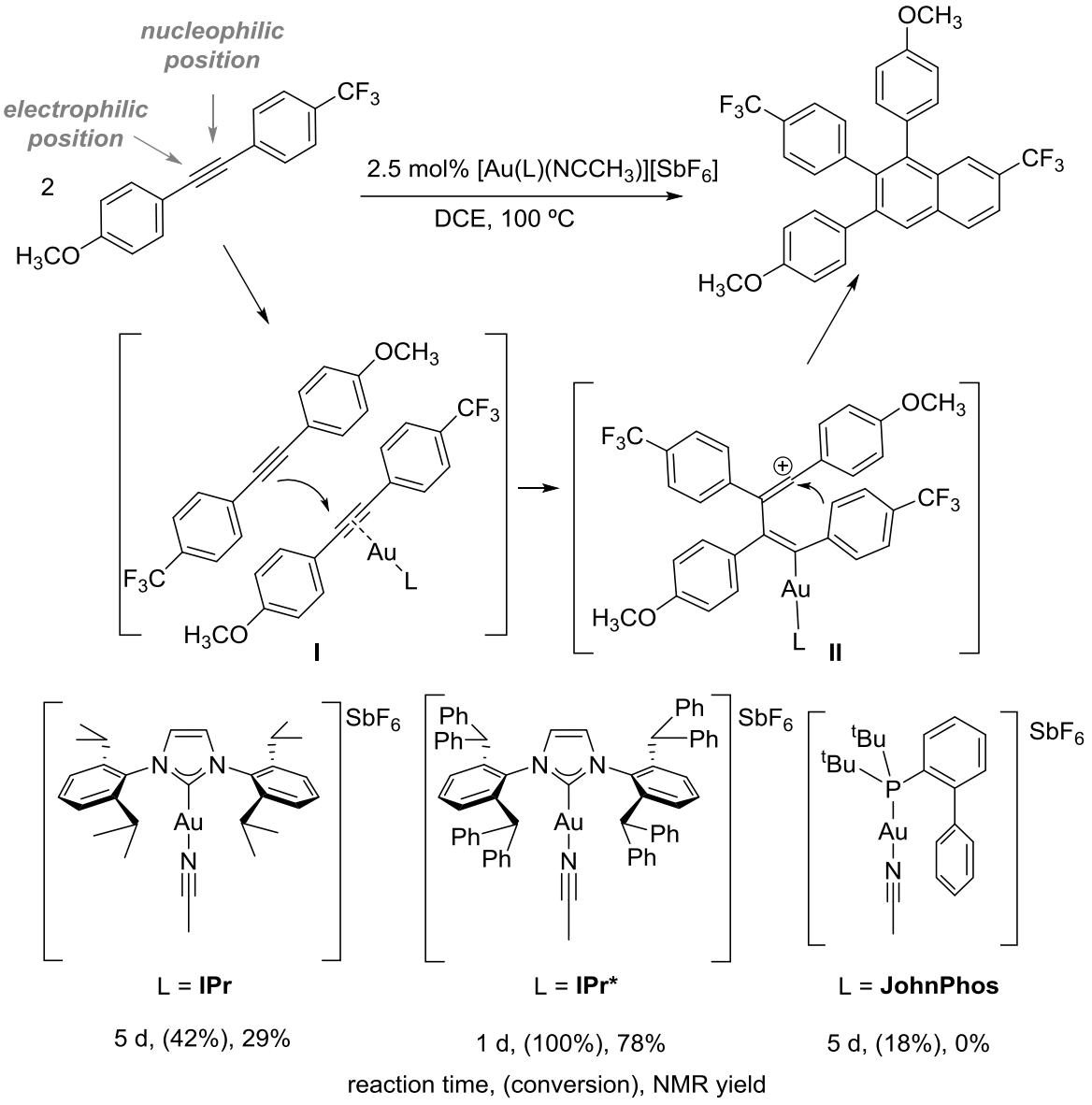
Hashmi and co-workers have reported different gold-catalysed transformations where the use of the sterically hindered IPr* ligand (**NHC-11**) translates into a catalytic activity improvement.[115] An example of this is the gold catalysed intermolecular cyclisation of furans and ethynyl aryl ethers to afford 2-phenoxyphenols (Scheme 46).[115] A comparison of the activity of different [Au(NHC)Cl] complexes in combination with $NaBAr^F$ showed that [Au(IPr*)Cl] (**NHC-11**) was more efficient than the analogous system with IPr.[115] The authors further optimised the reaction conditions using the [Au(IPr*)Cl]/$NaBAr^F$ system and successfully synthesised a range of 2-phenoxyphenols. The bulkier IPr** (**NHC-12**, %V_{bur} = 55.4)[116] ligand was shown to be a good ligand for the intramolecular version of this transformation.[117]

Scheme 46. Comparison between Au-IPr and Au-IPr* complexes in the intermocular cyclisation of furans and ethynyl aryl ethers.



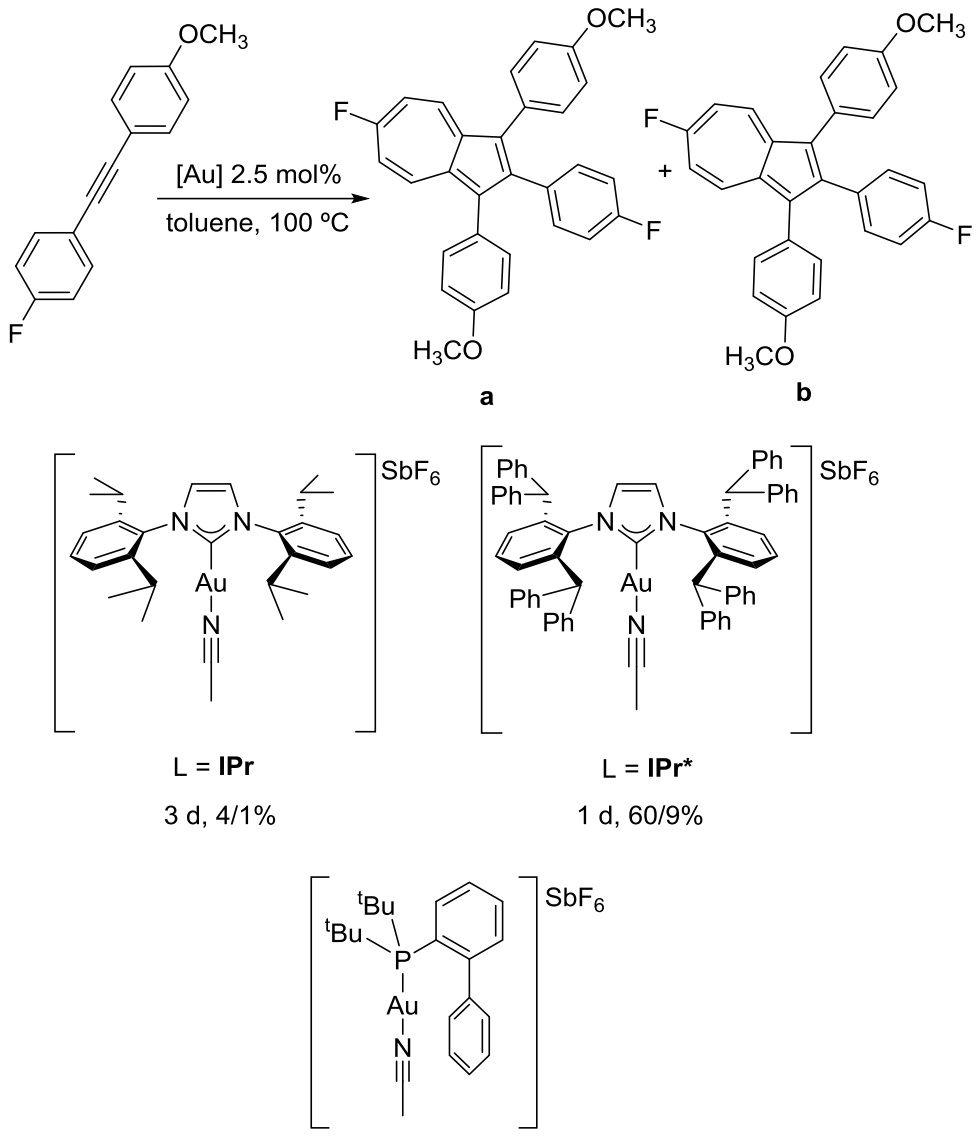
IPr* (**NHC-11**) was also a better ligand than IPr in the dimerization of push-pull diarylalkynes using well-defined cationic gold catalysts (Scheme 47). The corresponding naphthalene derivative was obtained in higher yields, after shorter times, when the Au-IPr* complex was employed.[118] In this process, a single regioisomer was obtained with alternating substituents in the naphthalene core. The formation of this product was rationalised based on the alkyne electronic nature and the stability of the proposed vinyl cation intermediate (Scheme 47). Alkynes with a decreased electronic polarisation afforded mixtures of products and alkynes where the electron-donating aryl group was replaced by alkyl groups did not undergo dimerisation, presumably due to the lower stability of the vinyl cation intermediate. [118]

Scheme 47. Dimerisation of diarylalkynes promoted by Au-NHC species.



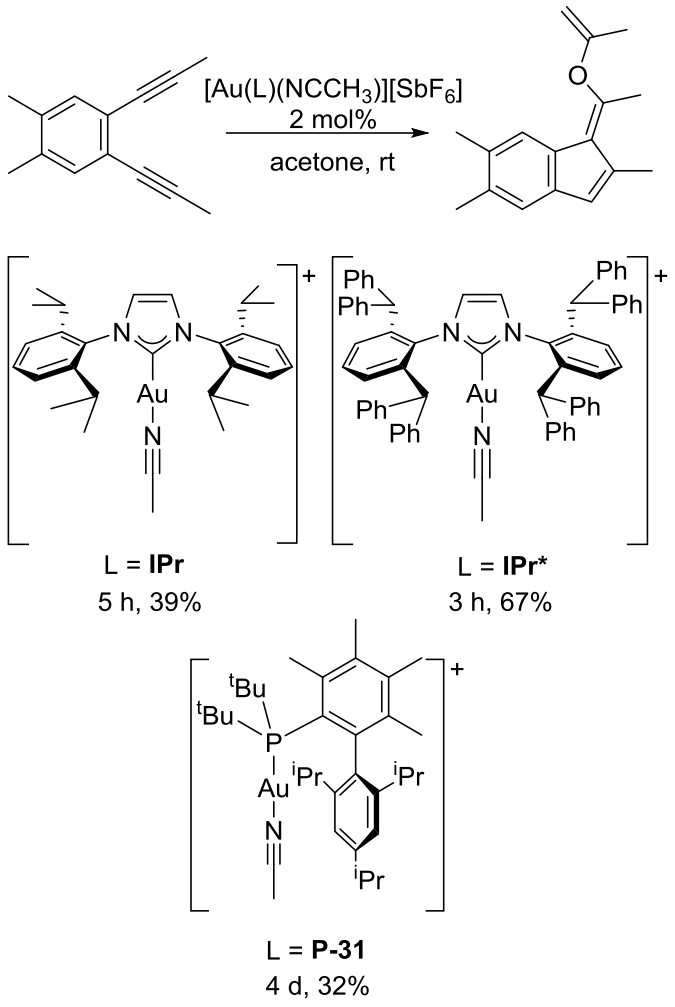
If diarylalkynes where the electron-deficient ring contains F atoms in *ortho* or *para* positions or symmetrical diarylalkynes are employed, azulenes are obtained (Scheme 48).[119] The formation of these products is rationalised based on the different electronic nature of the alkynes. The generation of a vinyl cation intermediate analogous to **II** in Scheme 47 is proposed. Then, the attack of the vinyl cation by the less electron ring would occur from the C directly connected to the alkyne, affording a 5-mebered ring. In this transformation, the bulky IPr* (**NHC-11**) ligand also outperformed IPr (**NHC-1**). The catalytic activity of other catalytic systems using [Au(L)Cl]/$AgSbF_6$ containing ligands such as asymmetrical NHCs, triphenylphosphine or phosphites did not afford the desired product.[119]

Scheme 48. Gold-catalysed synthesis of azulenes.



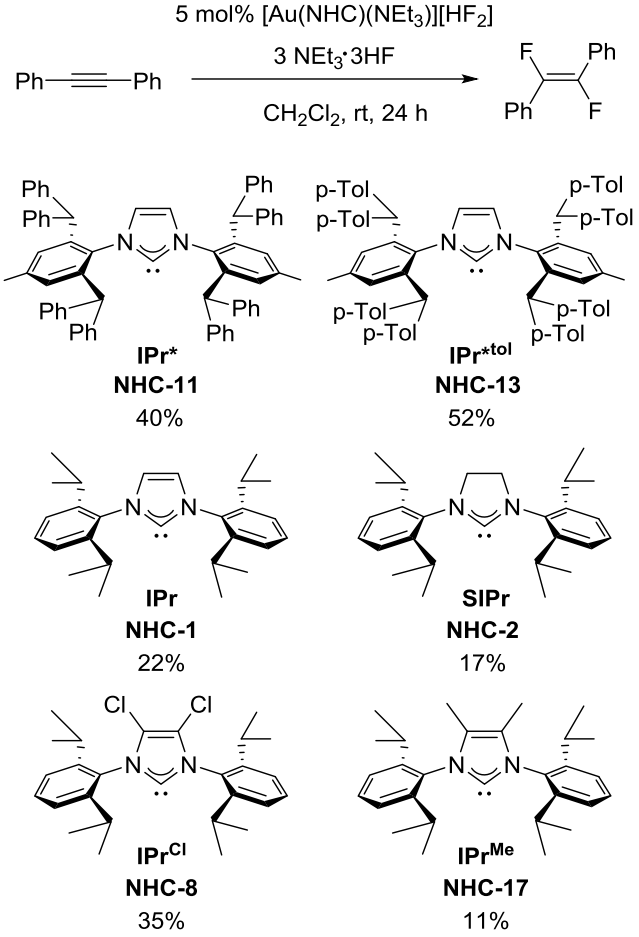
[Au(IPr*)(NCCH$_3$)]SbF$_6$ showed also a higher catalytic activity than the corresponding IPr-gold analogues in the cyclization of 1,5-diynes with ketones to afford fulvene vinyl ethers (Scheme 49).[120]

Scheme 49. Gold promoted fulvene vinyl ethers synthesis.



[Au(NHC)(NEt_3)][HF_2] complexes catalysed the hydrofluorination of diphenylacetylene with NEt_3·3HF.[108] The conversion was affected by the NHC ligand employed with the highly sterically demanding IPr* (**NHC-11**) and IPr*^{tol} (**NHC-13**) carbenes being more efficient (40 and 52% conversion, respectively) than other IPr-derivatives such as IPr (**NHC-1**, 22%), SIPr (**NHC-2**, 17%) IPr^{Cl} (**NHC-8**, 35%), and IPr^{Me} (**NHC-17**, 11%) (Scheme 50).[108] In agreement with an earlier report by Sadighi and co-workers, amongst the three IPr-based species, the less e-rich carbene, IPr^{Cl}, gave the higher reaction yield (Scheme 44, section 3.1.1.1).[107]

Scheme 50. Sterically hindered NHC ligands used in the gold-catalysed hydrofluorination of alkynes.



The synthesis of the 'ITent' (Tent = tentacular) series of NHC ligands: IPent (**NHC-14**), IHept (**NHC-15**), INon (**NHC-16**) allowed the study of the effect of the alkyl chain length on the *N*-aromatic ring in gold catalysis.

Electronic and steric analyses indicate that increasing the length of the alkyl chain translates into an increase of the $\%V_{bur}$ and the electron donating ability in the series IPr<IPent<IHept. This effect is negligible from IHept to INon, where the extra carbon atoms are too far from the metal centre to exert a strong effect (Figure 8).[121] The corresponding [Au(ITent)NTf_2] (NHCs **14**-**16**) complexes were prepared and their catalytic activity was evaluated, and compared to that of [Au(IPr)NTf_2], in the hydration of phenylacetylene and 4-methoxybenzonitrile, and in the synthesis of homoallylic ketones from diphenylacetylene and allyl alcohol. In all cases, the [Au(ITent)NTf_2] complexes were less active than [Au(IPr)NTf_2] affording lower conversions. The three Au-ITent complexes (NHCs **14**-**16**) showed different activity depending on the transformation. No electronic or steric trend was found for the alkyne hydration reaction: IHept was found to perform better than IPent and INon, which afforded similar yields. In the case of nitrile hydration and the synthesis of homoallylic ketones, a detrimental effect of the length increase was found, with IPent being the most efficient ligand. [121]

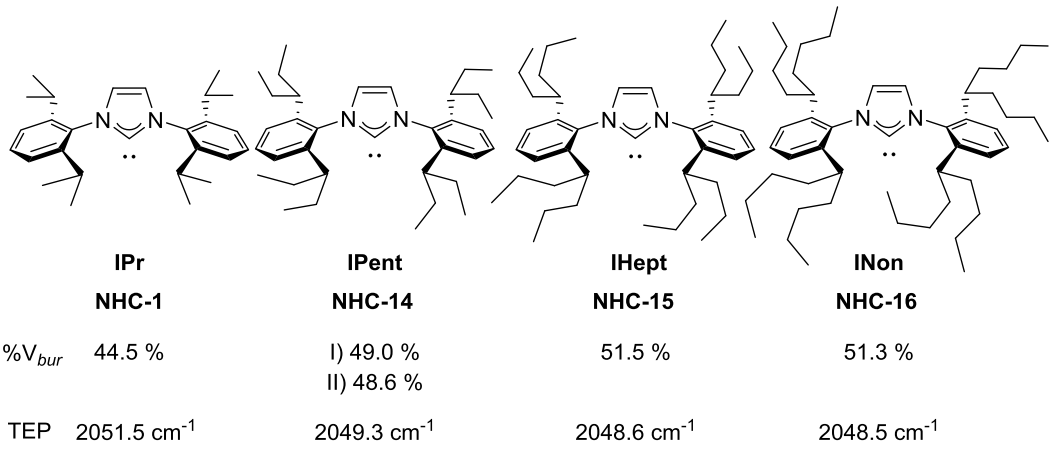


Figure 8. ITent series of NHC ligands

3.1.2 *N*-aryl NHC derivatives

Examples of other *N*-aryl NHC derivatives employed in gold catalysis will be discussed in this section (Figure 9). *N*-aryl NHC ligands tend to be less electron donating than *N*-alkyl derivatives and are usually more sterically hindered ligands, affording steric protection of the metal centre.[12,13,30]

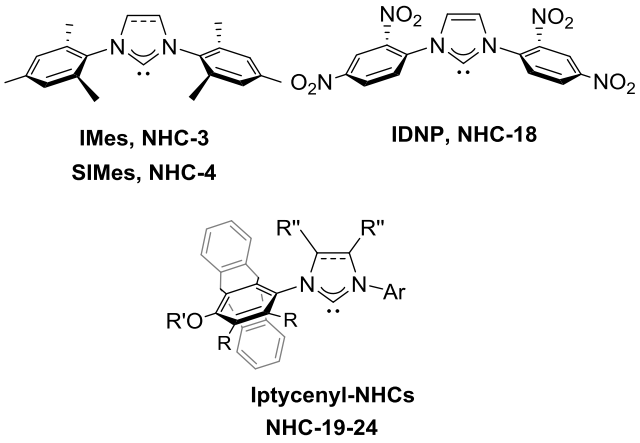


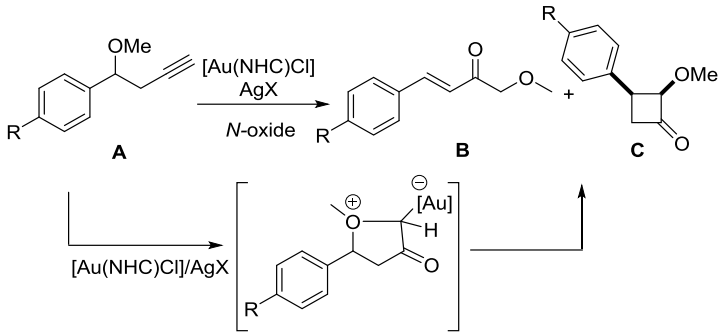
Figure 9. N-aryl NHC ligands discussed in this section

IMes (**NHC-3**) and SIMes (**NHC-4**) are much less frequently used in gold catalysis compared to IPr derivatives. They are often found in optimisation tables but they are usually outperformed by other NHC ligands. However, there are some transformations where the mesityl derivatives have proven to be superior to the IPr derivatives. The use of IMes and SIMes in gold catalysis has been reviewed previously.[122,123]

Interestingly, IMes (**NHC-3**) and SIMes (**NHC-4**) have been found to be very efficient ligands in some gold-catalysed oxidative processes. The gold catalysed oxidative rearrangement of homopropargylic ethers in the presence of pyridine *N*-oxide affords α,β-unsaturated carbonyl compounds[124] or cyclobutanones,[125] depending on the electronic properties of the starting material and the gold

complex employed (Table 2). Homopropargylic ether **A**, and derivatives with electron withdrawing substituents in the aromatic ring were transformed into compounds **B** (Table 2, entries 1-2). Product **B** was obtained in higher yield when IMes (**NHC-3**) was used as a ligand. Interestingly, when the starting material contained an electron-rich aromatic ring, the formation of cyclobutane **C** was also observed. Using **A-OMe** (Table 2) as precursor, higher selectivity towards the formation of the cyclobutane product was obtained with the Au-IMes precatalyst in comparison to Au-IPr (Table 2, entries 3-4).[124,125] Species **A** and **B** are proposed to be obtained via the formation of an α-oxo gold carbenoid intermediate, which could be stabilised by the IMes fragment, since this ligand is affording better conversions in all the cases.

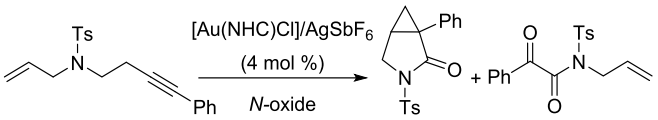
Table 2. Au-catalysed oxidative rearrangement of homopropargylic ethers.



entry	R	NHC	Time (h)	Yield **B** (%)	Yield **C**(%)
1	H	**IPr**	7	48	-
2		**IMes**	3.5	63	-
3	OMe	**IPr**	22	11	36
4		**IMes**	5	10	50

Additionally, the same methodology was applied to *N*-allylynamides (Table 3). In this case, two different products can be obtained: bicyclo[3.1.0]hexane derivatives (**B**, Table 3) or 1,2-dicarbonyl compounds (**C**, Table 3).[126] While all the ligands evaluated afforded a mixture of both species, phosphine ligands (PPh_3, JohnPhos and Cy-JohnPhos) gave compound **C** as a major product (entries 1-3, Table 3). In contrast, NHC ligands (IPr, **NHC-1**; IMes, **NHC-3**) favoured the formation of the bicycle **B** (entries 4-5, Table 3). Between them, a much higher selectivity was obtained with IMes (**NHC-3**) and this ligand was employed to develop the reaction scope.[126]

Table 3. Oxidative cyclopropanation of N-allylynamides.



A **B** **C**

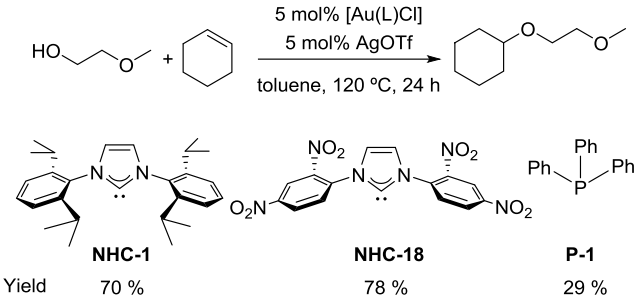
entry	L	Time (h)	Yield **b** (%)	Yield **c** (%)
1	**PPh_3**	3.5	39	60
2	**JohnPhos**	2.5	37	55
3	**Cy-JohnPhos**	3.2	47	50
4	**IPr**	7.0	48	31
5	**IMes**	1.0	76	21

Additionally, IMes (**NHC-3**) and SIMes (**NHC-4**) have been shown to be outstanding ligands in gold catalysed reactions of enynal and enynones with alkynes to synthesise polycyclic structure in the presence of Selectfluor.[123,127-129]

Sato, Oi and co-workers studied the effect of nitro substitution in the *N*-aryl ring of NHCs.[130] IDNP (**NHC-18**), bearing two *N*-2,4-dinitrophenyl groups was characterised and evaluated as a ligand in gold catalysis. As expected, IDNP was found to be less electron-rich than IPr (**NHC-1**), and presented similar donating properties to PPh_3 as revealed by IR spectroscopic studies of the $\nu_{av}(CO)$ stretching frequencies of the corresponding $[RhCl(NHC)(CO)_2]$ complexes. The steric volume of (**NHC-18**) is, however, closer to IPr (**NHC-1**). The σ-donor and π-acceptor contributions to the electronic properties of IDNP (**NHC-18**) were studied by calculating the energy levels of the corresponding orbitals. These calculations show that (**NHC-18**) is a weaker σ-donor and stronger π-acceptor than IPr.[130]

The activity of [Au(**NHC-18**)Cl]/AgOTf in the intermolecular hydroalkoxylation of cyclohexene was evaluated and compared to that of complexes bearing IPr (**NHC-1**) and PPh_3 (**P-1**) (Scheme 51). The catalytic activity of the complex containing IDNP (**NHC-18**) was found to be higher than that of the Au-IPr (**NHC-1**) complex and much higher than that of the Au-PPh_3 (**P-1**) derivative.[130]

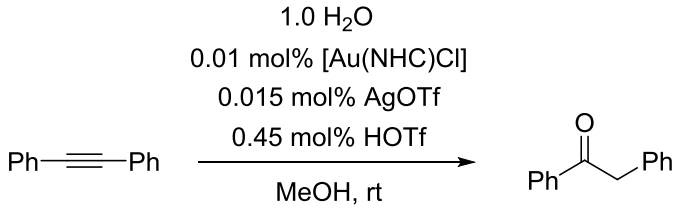
Scheme 51. Au-IDNP complex in catalysis.

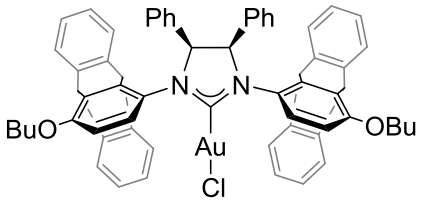


This reaction is further improved, under slightly different conditions, using benzimidazole ligands[131] and triazole derivatives containing NO_2[132] (see sections 3.1.2 and 3.5).

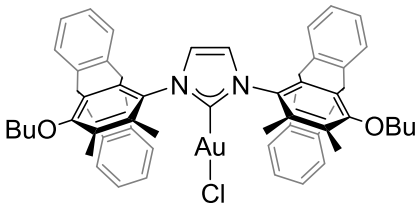
Plenio evaluated the effect of including very bulky iptycenyl groups in the NHC architecture in gold-catalysed alkyne hydration reactions. Six [Au(NHC)Cl] complexes containing ligands with different steric properties (**NHCs 19**-**24**) were prepared and their catalytic activity was evaluated.[133] The study revealed a catalytic activity enhancement with the increased steric bulk. Complexes with four triptycene units, [Au(**NHC-23**)Cl] and [Au(**NHC-24**)Cl] were the most active of the series, affording the highest yields (Scheme 52). Kinetic analysis showed that complex [Au(**NHC-24**)Cl], with a more electron-donating NHC ligand, gave higher reaction rates in comparison to [Au(**NHC-23**)Cl].[133] This pre-catalyst was found to be more efficient than other NHCs- and phosphine-gold complexes.[52] These bulky ligands could favour the protodeauration step, and prevent the formation of digold-off-cycle species.

Scheme 52. [Au(NHC)Cl] complexes with bulky iptycenyl subtituents in alkyne hydration.



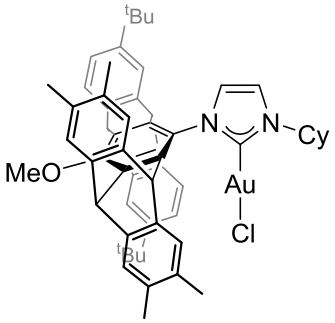


[Au(NHC-19)Cl]

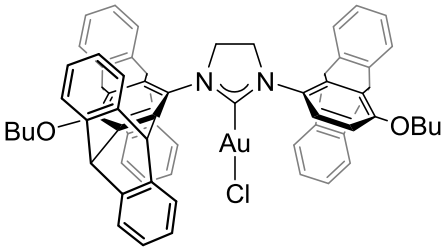


[Au(NHC-20)Cl]

4 h, GC yield	2%	11%
21 h, GC yield	22%	93%

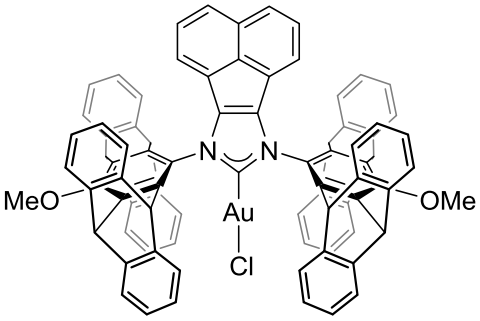


[Au(NHC-21)Cl]

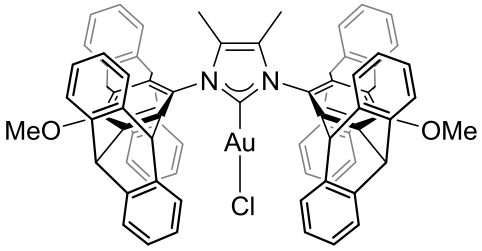


[Au(NHC-22)Cl]

4 h, GC yield	-%	3%
21 h, GC yield	6%	52%



[Au(NHC-23)Cl]



[Au(NHC-24)Cl]

4 h, GC yield	37%	60%
21 h, GC yield	>99%	>99%

3.1.3 *N*-alkyl NHC derivatives and other wingtip modifications

As mentioned earlier, *N*-alkyl substituted NHCs tend to be more electron-donating than the *N*-aryl derivatives. Depending on their substituents, they also have a higher tendency to dimerise[134] and they often afford less stable gold complexes. These factors might explain why they are less common in the literature. Some examples are discussed below (Figure 10).

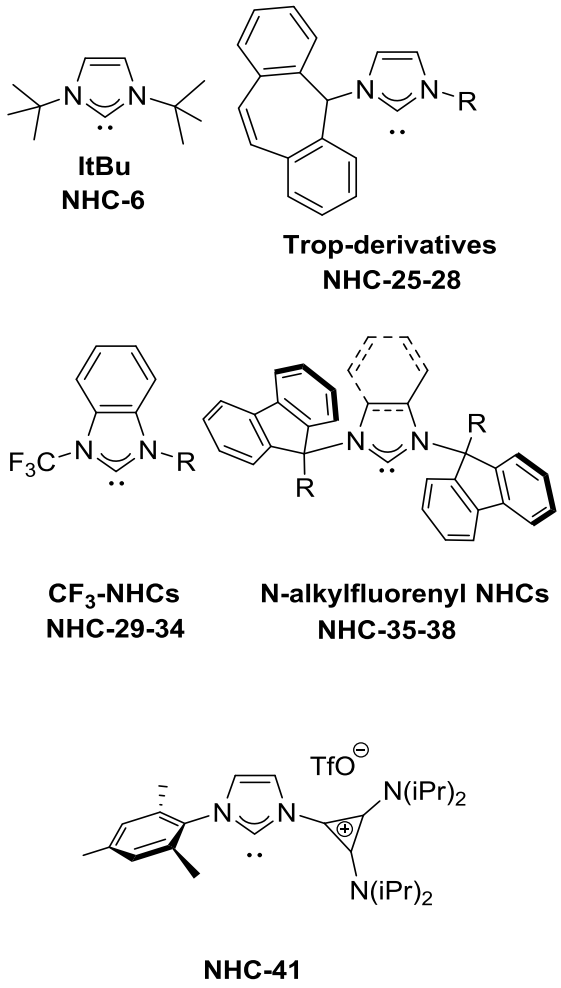


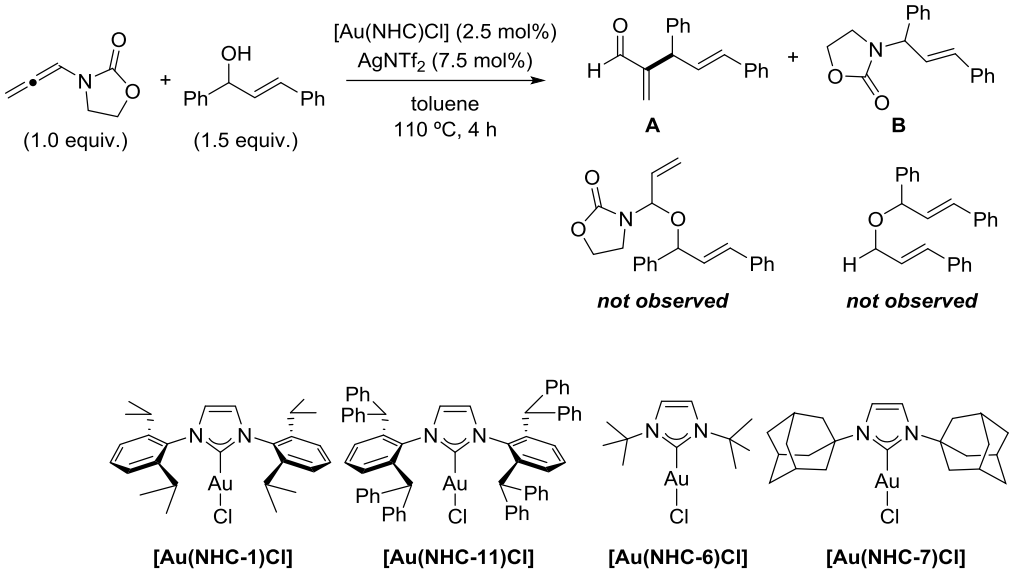
Figure 10. N-alkyl substituted NHC ligands

ItBu (**NHC-6**) is more electron-donating (TEP = 2050.1 cm^{-1})[21] and less bulky (%V_{bur} = 39.6)[30] than IPr (**NHC-1**, TEP = 2051.5 cm^{-1}; %V_{bur} = 45.4).[30,100] Au-ItBu species have been shown to be more efficient than the analogous Au-IPr complexes in some transformations.

Au-NHC species allowed for the development of the intermolecular α-allylation of enals and enones by condensation of allenamides and allylic alcohols.[135] Au-NHC pre-catalysts afforded the desired product **A** in higher yields and with less side-products than Au-phosphine complexes (Scheme 53). IPr (**NHC-1**) and ItBu (**NHC-6**) were better ligands than IPr* (**NHC-11**) and IAd (**NHC-7**) as shown in Scheme 53. When the well-defined Gagosz complexes, [Au(IPr)NTf_2] and [Au(ItBu)NTf_2], were employed, **A** was

obtained in higher yields with the latter (70% and 84% respectively) and the reaction scope was developed with the ItBu-system.[135]

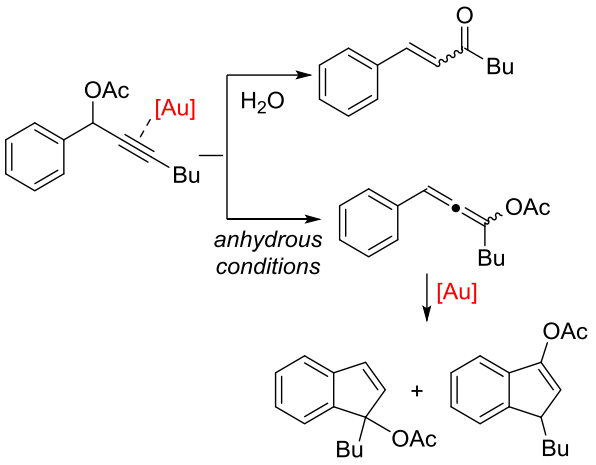
Scheme 53. Au-NHC catalysed α-allylation of enals with allylic alcohols



Yield of product **a**	97%	71%	94%	65%
Yield of side-product **b** (based on the alcohol)	35%	53%	37%	57%

The gold-catalysed rearrangement of propargylic acetates can afford different products depending on the catalyst system and reaction conditions. These transformations have been thoroughly studied.[112,136,137] Under aqueous conditions, α,β-unsaturated ketones are the main reaction product (Scheme 54). The activity of a range of [Au(NHC)NTf_2] complexes (**NHC-1**-**7**) has been evaluated and [Au(ItBu)NTf_2] (**NHC-6**) was found to be the most efficient (89% vs 79% yield with IPr).[112]

Scheme 54. Gold-catalysed rearrangement of propargylic acetates



Imidazolium salts containing *N*-dibenzotropylidene substituents were prepared and coordinated to gold (**NHCs 25**-**28**, **Figure 11**). The corresponding [Au(NHC)(NTf_2)] complexes were prepared and their activity in the hydration of diphenylacetylene was evaluated.[138] Only the complex containing **NHC-28** (trop/dipp) was able to promote this transformation, however the activity was much lower than that of the related Au-IPr complex.[138]

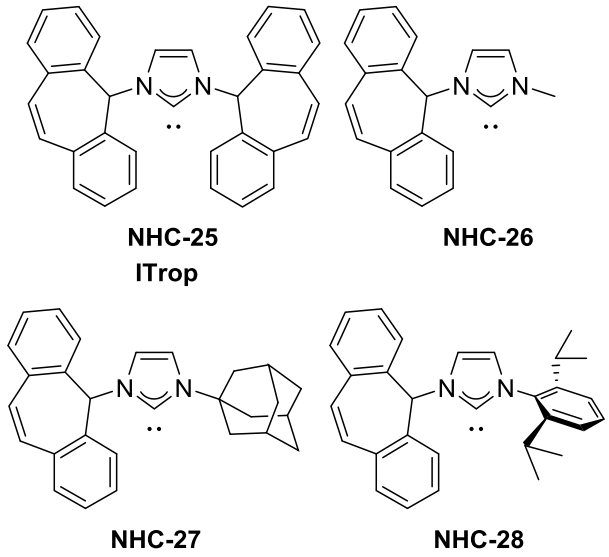
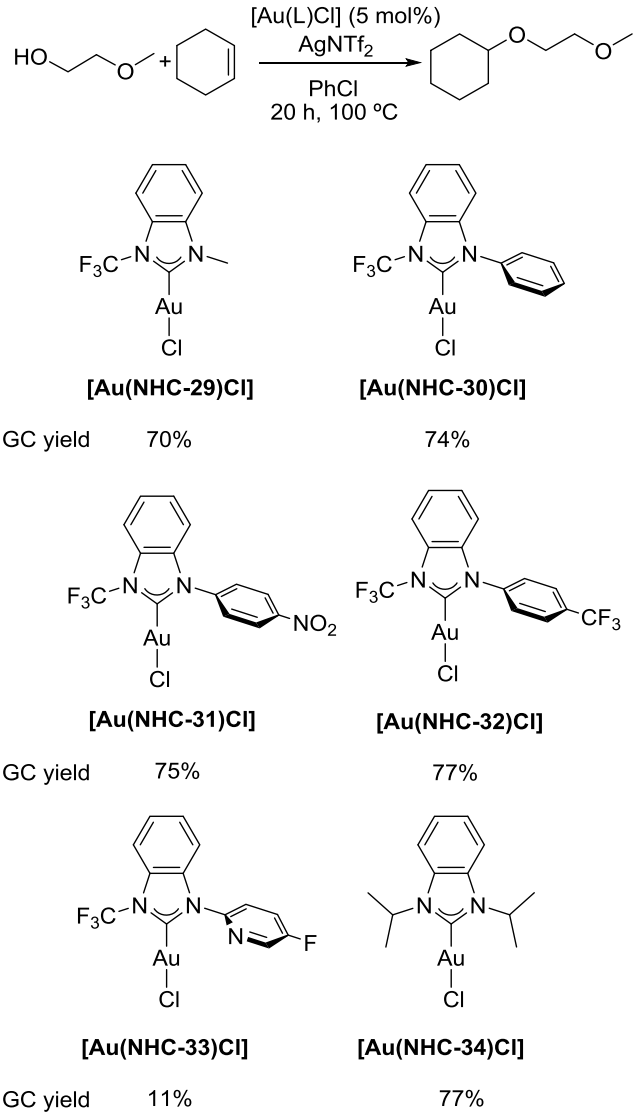


Figure 11. Trop-NHC ligands.

Togni and co-workers explored the properties of *N*-trifluoromethyl benzimidazole-based NHCs (**NHC-29-33**).[131] The TEPs of the *N*-CF_3 NHC ligands were higher (2058-2060.8 cm^{-1}) than that of **NHC-34** (2053.3 cm^{-1}) and much higher than the values for IPr (**NHC-1**, 2051.5 cm^{-1}) and SIPr (**NHC-2**, 2052.2 cm^{-1}). The π-accepting properties of these ligands were evaluated by means of ^{77}Se NMR spectroscopy of the corresponding [Se(NHC)] complexes and electrochemical measurements of [Rh(NHC)(COD)Cl] complexes. All the data show that the presence of the CF_3 groups decreases the carbene σ-donating properties while increasing their π-accepting ability.[131] The gold complexes were employed as catalysts in the hydroarylation of cyclohexene, since NHC-gold complexes containing π-acceptor ligands had been demonstrated to be active in this transformation (see section 3.1.2 and 3.5).[130,132]
All of the complexes, except the one bearing a pyridyl substituent, were very efficient in this transformation under the conditions shown in Scheme 55 (70-77 % yield). However, the catalyst activity was not related to the NHC π-accepting properties. In fact, the *N*-CF_3 NHC-Au complexes afforded similar yields to that obtained when complex [Au(**NHC-34**)Cl] was employed (77%).[131] Under these conditions, all the complexes containing benzimidazole ligands were more efficient than the Au-

IPr system (35%); Au-PPh_3 afforded 76% yield, and Au-IDNP (**NHC-18**) gave 64% yield (see section 3.1.2).

Scheme 55. N-Trifluoromethyl NHC-gold complexes used in catalysis.



Blanc, Brenner, Matt and co-workers reported the synthesis and catalytic activity of gold(I) and gold(III) complexes containing *N*-alkylfluorenyl-substituted NHC ligands.[139,140] Relevant to this review, we will focus on the catalytic activity of the [Au(NHC)Cl] derivatives (Figure 12). Complexes containing imidazolin-2-ylidene (**NHC-35**) and imidazolidin-2-ylidene (**NHC-36**) ligands showed free rotation around the *N*-C(alkylfluorenyl) bond; in contrast, benzimidazolium derivatives, ([Au(**NHC-37**)Cl] and [Au(**NHC-38**)Cl]), showed restricted rotation, with the alkyl chains directed towards the metal centre.

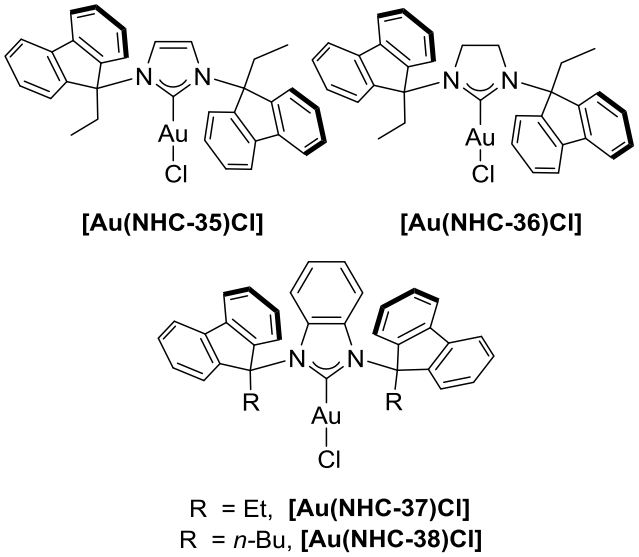
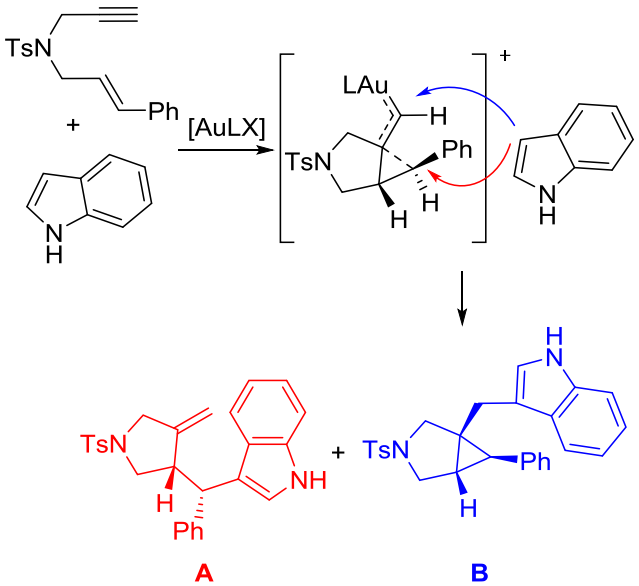


Figure 12. Au(I) complexes containing confined NHC ligands (**NHC 35**-**38**).

The authors evaluated the activity of [Au(NHC)Cl] (**NHC**- **35**-**38**) complexes in the rearrangement of 1,6-enynes in the presence of indole.[140] This transformation is known to afford two different products, **A** and **B**, depending on the position where the indole nucleophilic attack occurs (Scheme 56).[140-142]

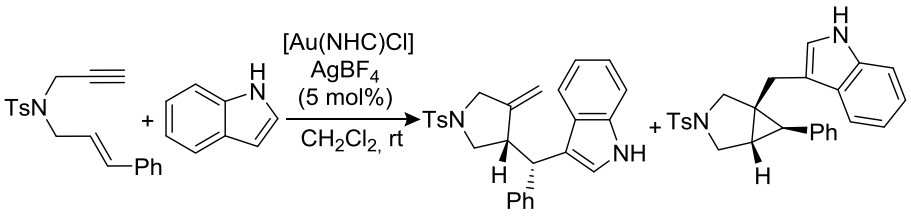
Scheme 56. Gold-catalysed 1,6-enyne rearrangement in the presence of indole.

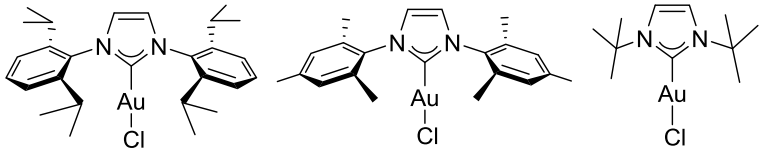


Species **A** is primarily obtained when bulky phosphines or phosphites are employed as ligands,[143] while classical NHCs such as IPr (**NHC-1**), IMes (**NHC-3**) or ItBu (**NHC-6**) favour **B** although with low selectivity. Sterically demanding acyclic diamonocarbene ligands, **NHC**-**39** and **40** (ADC, see section 3.6), allowed for a selectivity switch favouring the formation of **A** over **B.**[144] A remarkable selectivity improvement towards species **A** was obtained when [Au(NHC)Cl] (**NHC 35**-**38**) were employed (Scheme 57).[140] The different reactivity was attributed to steric factors. To justify this behaviour, the steric maps of

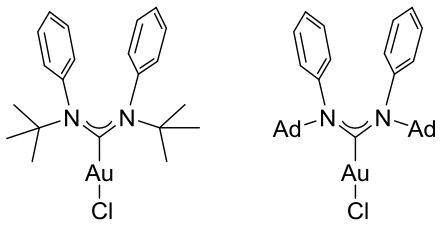
complexes [Au(NHC)Cl] (**NHC 35**-**38**) were calculated showing that the most selective catalysts were those with more sterically encumbered NHC ligands. Thus, these ligands would favour the indole nucleophilic attack in the remote position, far from the gold center.

Scheme 57. Ligand dependant selectivity on the gold promoted addition of indole to a 1,6-enyne.

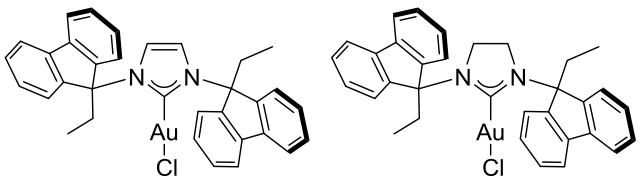




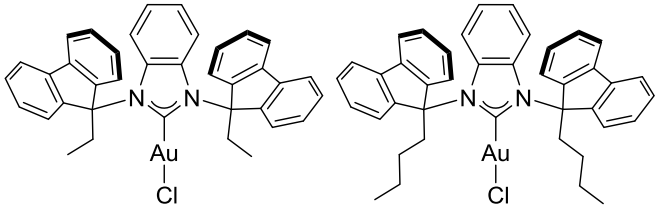
	[Au(NHC-1)Cl]	[Au(NHC-3)Cl]	[Au(NHC-6)Cl]
Ratio A:B	25:75	45:55	43:57
Yield of A/B %	14/43	32/40	29/38



	[Au(NHC-39)Cl]	[Au(NHC-40)Cl]
Ratio A:B	51:49	82:18
Yield of A/B %	39/37	64/14



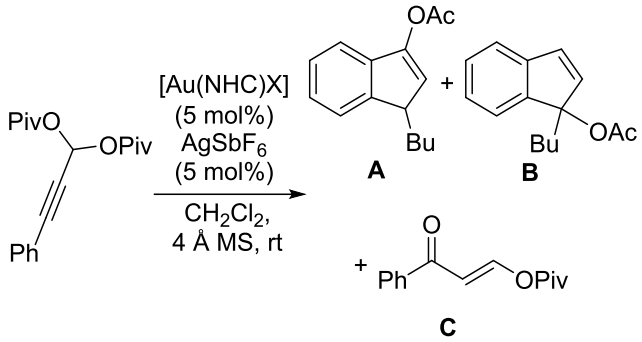
	[Au(NHC-35)Cl]	[Au(NHC-36)Cl]
Ratio A:B	99:1	99:1
Yield of A/B %	49/-	34/-



	[Au(NHC-37)Cl]	[Au(NHC-38)Cl]
Ratio A:B	89:11	99:1
Yield of A/B %	48/6	67/-

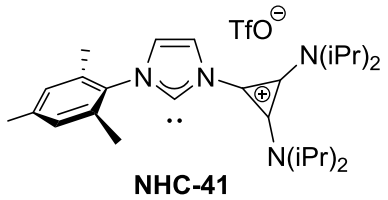
In a subsequent report, the authors exploited the steric properties of the **NHC-38** ligand to develop the regioselective synthesis of 1,3-indenes from 3-aryl propargylic gem-dipivalates.[139] The activity of different Au-NHC species was evaluated, finding that Au(**NHC-38**) was able to afford species **A** in high yield and selectivity, while the other NHC ligands employed afforded mixtures of species (Table 4).

Table 4. Ligand effect on the gold-catalysed synthesis of 1,3-indenes.



	Catalyst	Time (h)	Yield **A** (%)	Yield **B** (%)	Yield **C** (%)
1	**[Au(IPr)Cl]**	1	25	42	16
2	**[Au(IMes)Cl]**	0.25	10	5	28
3	**[Au(SIPr)Cl]**	0.75	20	55	18
4	**[Au(ItBu)Cl]**	0.25	45	28	10
5	**[Au(IAd)Cl]**	0.25	41	2	3
6	**[Au(NHC-38)Cl]**	0.5	85	6	-

Canac, César and co-workers synthesised a NHC ligand bearing a *N*-cationic substituent (**NHC-41**) (Figure 13).[145] The stereoelectronic properties of **NHC-41** were characterised. This carbene was found to be less donating than the analogous IMes ligand (**NHC-3**) (TEP = 2057 vs 2051 cm^{-1}, respectively) and more π-accepting, according to the δ_{Se} chemical shift of their corresponding selenoureas in the ^{77}Se NMR spectra (δ_{Se} = 112 and 27 ppm, respectively).[145] The catalytic activity of the [Au(**NHC-41**)Cl]/AgOTf system in intramolecular cyclisations was comparable to that of IPr (**NHC-1**).



NHC-41

Figure 13. N.Cyclopropenio-imidazolin-2-ylidene.

3.1.4 NHC Backbone modification

In addition to the ligands described in section 3.1.1.1., there have been other backbone modifications of imidazolylidenes (Figure 14).

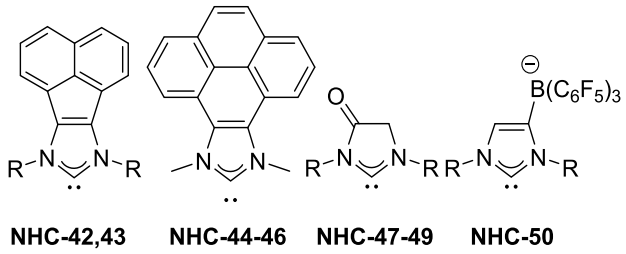


Figure 14. Examples of NHC with a modified backbone

3.1.4.1 NHC ligands with polyaromatic backbones

The incorporation of extended aromatic rings in the NHC backbone decreases the π-accepting properties of the carbenes, increasing, therefore, their σ-donating abilities. This feature has proven to be beneficial in some gold-catalysed transformations.

The catalytic activity of gold complexes containing acenaphthoimidazolydene NHC ligands (**NHC-42**, **43**) was evaluated by Tu and co-workers in the direct alkylsulfonylation of arylboronic acids with potassium metabisulfite and alkyl halides to afford sulfones (Figure 15).[146] Their activity was compared to that of Au-IPr (**NHC-1**) and Au-IMes (**NHC-3**) complexes. [Au(**NHC-42**)Cl] was found to be the most efficient catalyst of the series, affording the desired sulfone in 75 % isolated yield (Figure 15). Noteworthily, the Au-acenaphthoimidazolydene complexes were more efficient that their corresponding Au-IPr and Au-IMes analogues in all cases, indicating that stronger σ-donor ligands improve the catalytic activity in this transformation.[146] The protocol was applied to a wide range of substrates allowing for the synthesis of forty-two different examples of (hetero)aryl-alkyl, aryl-alkenyl, and alkenyl-alkyl sulfones.[146] When diaryliodonium salts were used instead of alkyl halides, diarylsulfones were obtained in the presence of Au-NHC complexes.[147] Au-acenaphthoimidazolydene complexes were again more efficient than their IPr and IMes analogues. By using this protocol, the authors were able to prepare sixty different diarylsulfones with high selectivity for the transfer of electron-rich and bulky aryl groups from the diaryliodonium salts.[147]

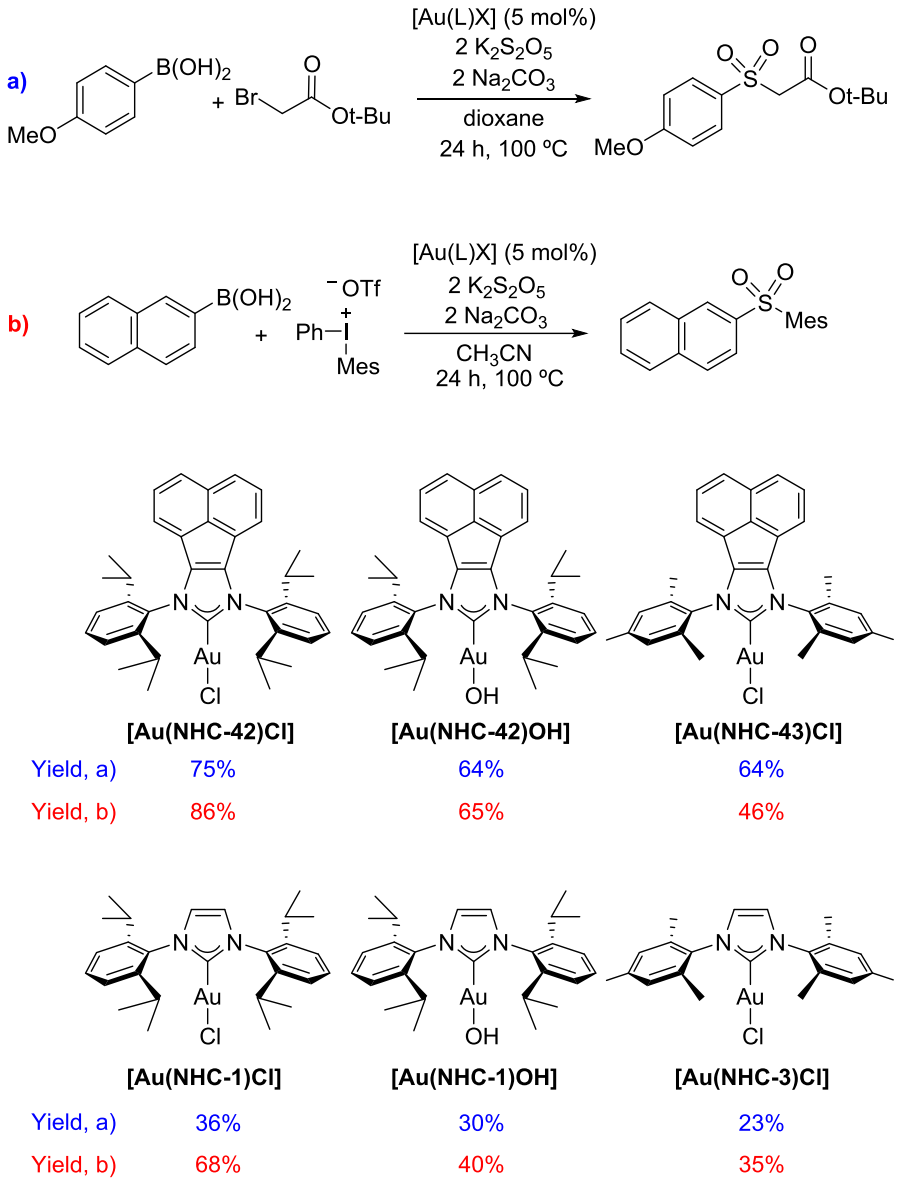
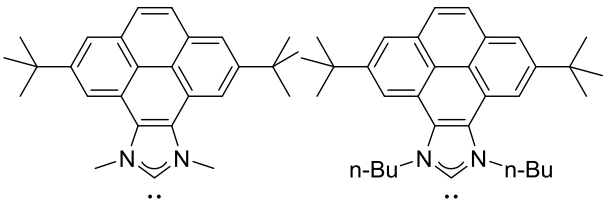
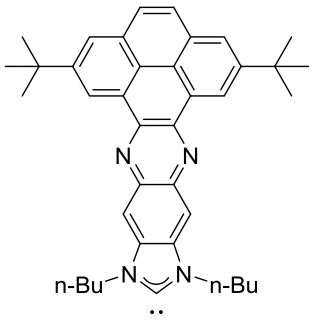


Figure 15. Catalytic activity of acenatphthoimidazolylidene gold complexes.

The implications of the π-stacking of polyaromatic NHC systems on catalysis have been studied. Gold complexes containing NHC ligands with fused polycyclic aromatic carbons (**NHC-44**-**46**, Figure 16) were prepared and their performance in the hydroamination of phenylacetylene was evaluated. The reaction rate and yield were improved by addition of pyrene to the mixture. This effect was attributed to π-stacking between the catalyst backbone and pyrene, avoiding the formation of catalyst self-aggregates.[148]



(NHC-44) **(NHC-45)**



(NHC-46)

Figure 16. NHC ligands with polyaromatic backbones

3.1.4.2 Switchable-backbone NHC ligands

The incorporation of an enolate backbone to form NHOCs (Figure 17) allows for tuning of the electronic properties of the NHC ligand by chemical postfunctionalisation since the anionic enolate form is more donating than the keto form.[149] Gold complexes containing this family of switchable carbenes have been prepared from isocyanide gold complexes.[150] The catalytic activity of gold-NHOC complexes (**NHC-47**-**49**, Figure 17) was tested using the cycloisomerisation of propargyl amides to alkylideneoxazolines and compared to that of Au-IPr species. While the yield that was obtained was similar with all of the complexes, the reaction rate was 3.5-4 times higher with Au-NHOC complexes, affording higher TOF values.[150]

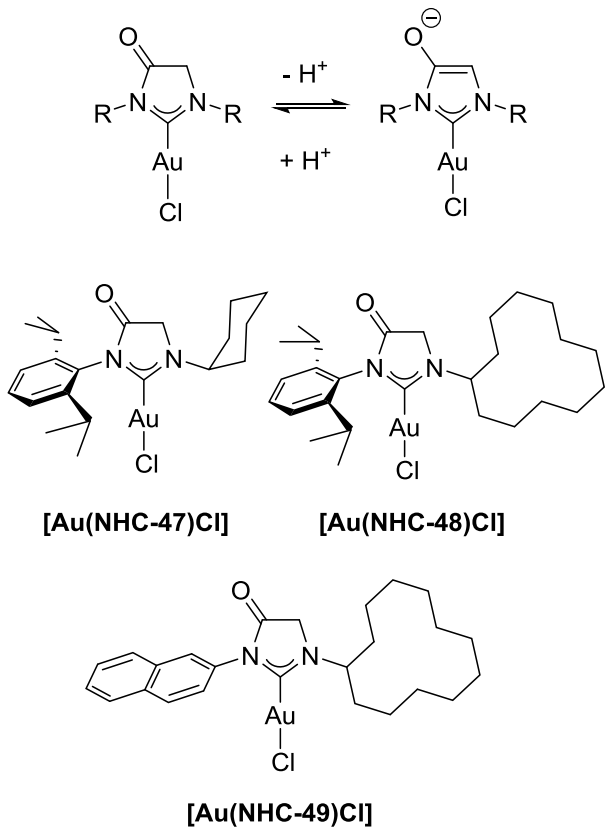


Figure 17. Au complexes bearing NHC ligands with switchable backbones

3.1.4.3 Anionic NHC ligands

Zwitterionic NHC carbenes containing weakly coordinating anionic borate fragments in the backbone (**NHC-50**) have been used as ligands in gold catalysis.[151,152] The neutral gold complexes [Au(**NHC-50**)(tht)][151] and [Au(**NHC-50**)(dms)][152] have proven to be active in the cycloisomerisation of enynes and hydration of alkynes, respectively. These catalysts did not require the addition of silver salts to promote such transformations (Figure 18).[151,152]

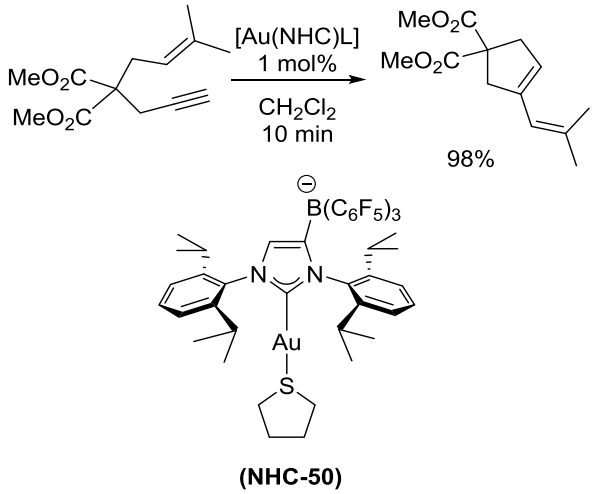


Figure 18. A gold complex containing a zwitterionic NHC carbene.

3.1.5 Water soluble NHC ligands

Using water as solvent for catalytic transformations is an attractive approach towards greener reactions. Since most of the gold complexes employed as catalyst are not water soluble, the structure of the ligands has often been modified to improve the complex solubility in aqueous media.

Although different strategies have been employed to increase the solubility of NHC-Au complexes in water, the incorporation of sulfonated groups in the structure has been the most widely employed approach. In this context, NHCs bearing *N*-alkyl sulfonated groups (e.g. **NHC-51**),[153] sulfonated IMes and SIMes analogues (**NHC-52**, **53**)[154] IPr-sulfonated derivatives (**NHC-54**),[155] or *N*-alkyl sulfonated NHCs with pyridine pendant groups (**NHC-55**)[156] have been prepared. Gold complexes containing these ligands have been used for alkyne hydration,[153-155] and cycloisomerisation[156] reactions in water/organic solvent mixtures (Figure 19).

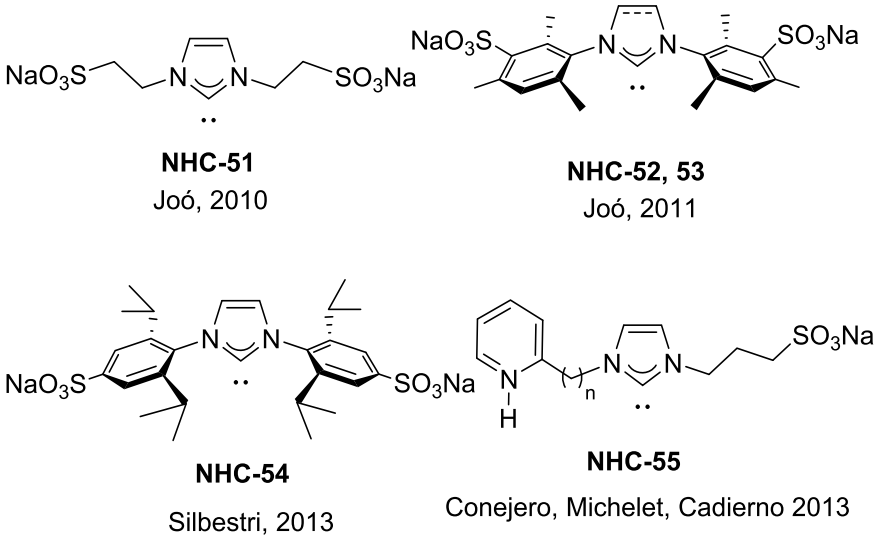


Figure 19. Representative examples of sulfonated-NHC ligands used in gold catalysis in water/organic solvent media.

A structure/activity study of water-soluble Au-NHC compounds in alkyne hydration was conducted both experimentally and theoretically.[157] Five different [Au(NHC)Cl] complexes containing sulfonated NHC ligands were tested (**NHC-54**,**56**-**59**, Figure 20). The Au-IPr-sulfonated derivative (**NHC-54**) was proven to be an efficient catalyst for alkyne hydration in water. The rest of the complexes were not active in water and mixtures of methanol and water were required in all cases. Kinetic analysis and DFT calculations showed that the gold complex catalytic activity was related to the NHC ligand steric hindrance, with higher yields obtained in shorter times with bulkier ligands.[157,158]

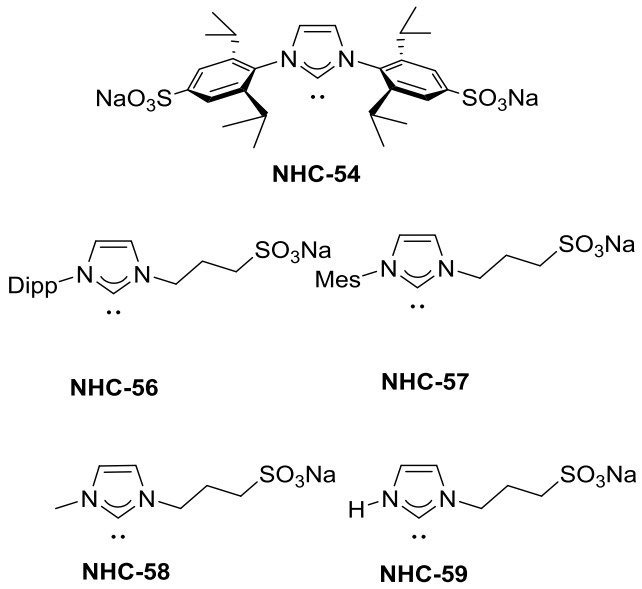


Figure 20. Water soluble sulfonated-NHC ligands employed in gold catalysed alkyne hydration.

NHC ligands containing ammonium salt groups have also been prepared and coordinated to gold.[159-161] A family of gold complexes containing unsymmetrical *N*-aryl, *N*-alkyl NHC ligands (e.g. **NHC-60**),[159] as well as an ammonium-salt-IMes derivatives (e.g. **NHC-61**) have been prepared (Figure 21).[160] These gold complexes were successfully employed in cycloisomerisation reactions in water.[159,160] Ammonium groups have been attached as well to IPr derivatives through triazole units (**NHC-62**, Figure 21).[161] These complexes were able to promote alkyne hydration in neat water.[161]

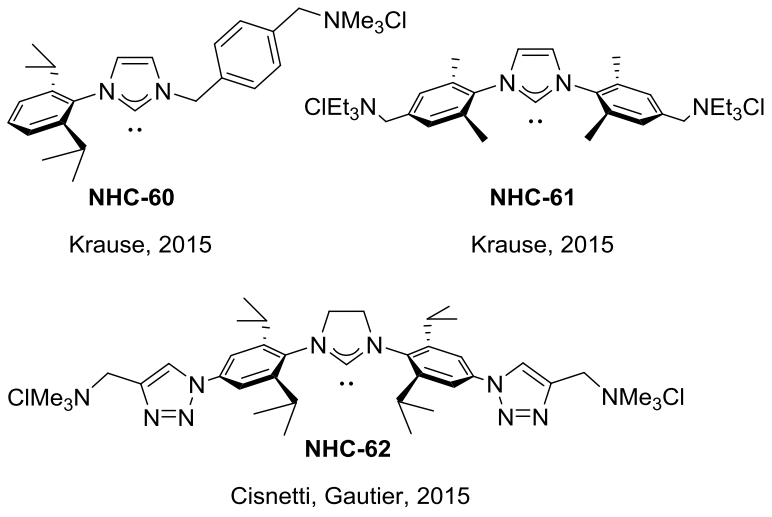
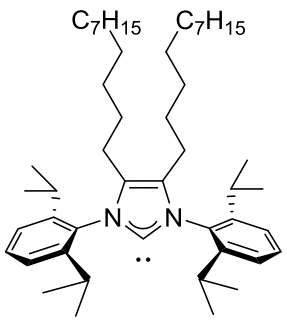


Figure 21. Representative examples of NHC ligands containing ammonium salts employed in gold catalysis in aqueous media.

Additional strategies to increase the solubility in water include backbone modulation to incorporate long alkyl chains to prepare a hybrid surfactant-NHC ligand (**NHC-63**, Figure 22).[162] Upon coordination

to gold and in the presence of a co-surfactant, this species promoted alkyne hydration reactions in water.[162]



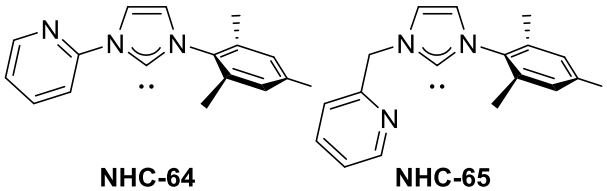
NHC-63
hybrid surfactant-NHC

Figure 22. Hybrid surfactant-NHC ligand

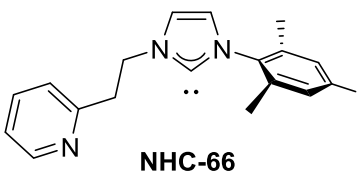
3.1.6 NHC ligands with pendant groups

The incorporation of pendant groups with donor atoms into the NHC structure can assist catalytic processes, usually by coordination to the metal centre or activation of substrates. *N*-[163,164](see section 3.1.5[156]) and *O*-donor[165-167] moieties have been attached to NHC ligands and their effect has been explored in gold catalysis. The most relevant results in this area are presented in this section.

Several NHC ligands with pendant pyridyl groups have been synthesised. Gold complexes containing **NHC-64**-**66** (Figure 23) were tested in the cycloisomerisation of an ω-alkynylfuran to afford isobenzofuranol. Coordination of the pyridine to the gold centre was only observed for complexes containing **NHC-65** and **NHC-66** when silver salts were added. In these cases, dimeric cationic gold complexes were formed which were proposed to be catalyst resting states.[163]



NHC-64 **NHC-65**

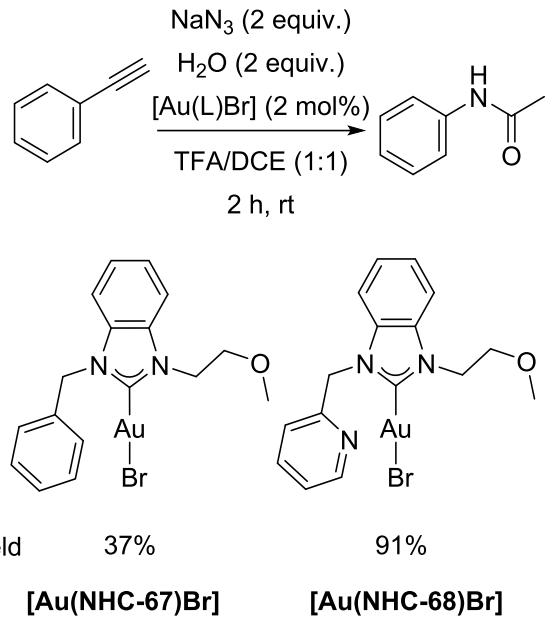


NHC-66

Figure 23. Pyridine functionalised NHC ligands employed in gold-promoted cycloisomersation reactions.

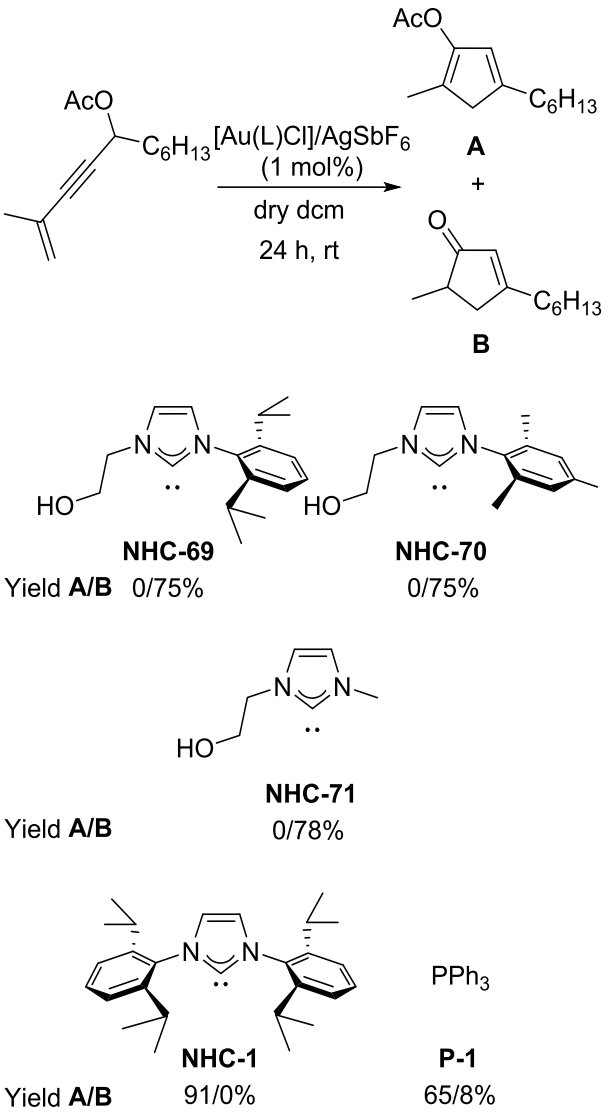
The effect of pendant pyridine groups has also been explored in benzimidazolydine NHC-gold complexes.[164] Two asymmetric gold-NHC complexes featuring *N*-benzyl (**NHC-67**) and *N*-CH_2pyridyl (**NHC-68**) groups were prepared. These gold complexes promoted the synthesis of secondary amides from terminal alkynes and sodium azide in the presence of water and trifluoroacetic acid (Scheme 58). The complex containing a pendant pyridine, [Au(**NHC-68**)Br], was found to be significantly more active than the phenyl counterpart. The pyridine role was proposed to be the activation of the incoming water molecule.[164]

Scheme 58. Effect of a pendant pyridine-NHC ligand on amide formation.



The catalytic performance of gold(I) and gold(III) complexes containing alcohol functionalised NHCs has been evaluated. For consistency, only the reactivity of gold(I) complexes will be discussed.[165] [Au(**NHC-69-71**)Cl] complexes promoted the tandem 3,3-rearrangement-Nazarov reaction of enynyl acetate to afford species **B** (Scheme 59).[165] Under the conditions shown in Scheme 59, complexes [Au(**NHC-69-71**)Cl] selectively afforded species **B** in the same yield (75-78%). The [Au(IPr)Cl]/$AgSBF_6$ or [Au(PPh_3)Cl]/$AgSF_6$ systems favoured the formation of species **A**. When wet solvents were employed, the hydrolysed species **B** was obtained in 92 % yield with PPh_3.[165] The presence of the pendant alcohol moiety in **NHC-69-71** was proposed to facilitate the hydrolysis step.

Scheme 59. Tandem 3,3-rearrangement-Nazarov reaction of enynyl acetate



The effect of carboxylate-functionalised NHC ligands in gold catalysed functionalisation of benzene and hexane with ethyl diazoacetate has been investigated (Figure 24, **NHC-72**-**75**).[167] When using benzene as the substrate, the activity of the complexes containing carboxylate groups was found to be lower (55-65% yield with complexes containing one carboxylate group; 11% yield with the complex containing **NHC-72**) than that of [Au(IPr)Cl] (>99%). Carboxylate complexes showed a different selectivity as well. When hexane was used as a substrate, selectivity towards secondary CH functionalisation was obtained with the NHC-carboxylate gold complexes. The origin of the lower activity and the selectivity was proposed to be due to weak coordination of the carboxylate group to the gold centre during the catalytic cycle, affording a gold-carbene tricoordinate intermediate. This species would be less reactive and steric hindrance would disfavour functionalisation of primary CH bonds. However, DFT calculations did not support this hypothesis.[167]

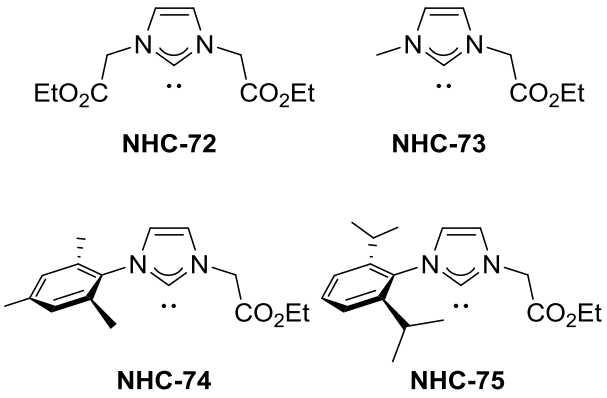


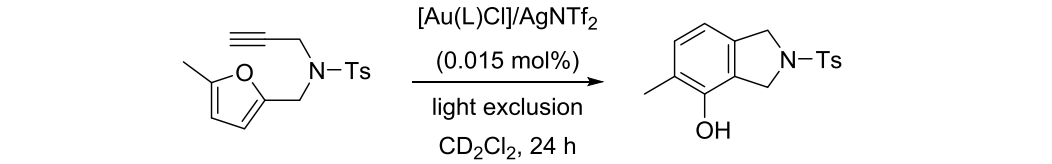
Figure 24. NHC ligands employed in gold-catalysed C-H functionalisation of aliphatic hydrocarbons with ethyl diazoacetate

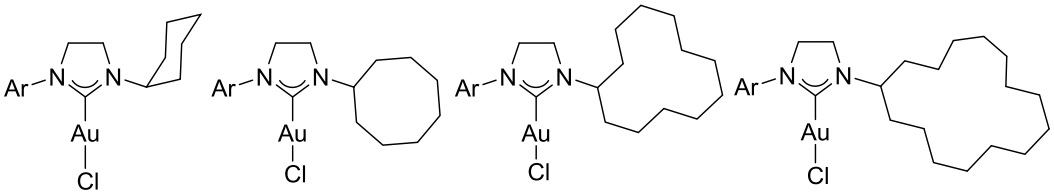
3.1.7 Unsymmetrical NHC ligands

The most commonly employed NHC ligands are symmetrically substituted. A reason for that might be the fact that the synthesis of symmetrical NHC ligands is straightforward from the corresponding anilines[94-96] and the synthesis of unsymmetrical NHC ligands require other strategies. In this section, studies focused on the effect of the unsymmetrical nature of NHC ligands in gold catalysis are described.

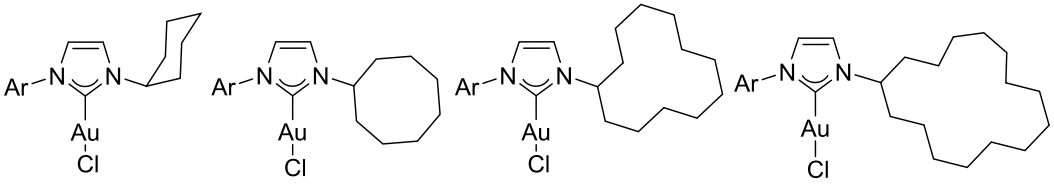
Using isocyanide gold complexes as precursors, Hashmi and co-workers synthesised a wide range of unsymmetrical NHC gold complexes and performed structure-activity catalytic studies.[168,169] Three families of Au-NHC complexes were prepared: saturated 5-membered ring- (**NHC-76**-**79**, Scheme 60); unsaturated-5-membered ring (**NHC-80**-**83**, Scheme 60) and *N*-heterocyclic-oxo carbenes (**NHC-84**-**87**, Scheme 60). All of the ligands were unsymmetrically substituted, with each of them bearing a *N*-diisopropylphenyl group and an *N*-alkyl chain of variable size. The impact of the heterocyclic core and the *N*-alkyl chain were explored in the transformation of furan-ynes to phenols using 1 equiv. of the corresponding [Au(NHC)Cl] complex and 1 equiv. of $AgNTf_2$ in the absence of light.[169] The family of saturated NHC ligands (**NHC-76**-**79**) afforded higher conversions compared to rest of the systems (Scheme 60). Kinetic analysis showed that, although initial reaction rates are slower when saturated NHCs are employed, these are more stable under the reaction conditions, giving higher TON values over time. The *N*-alkyl ring size did not directly correlate with the obtained conversion, however, the ligand containing a cyclopentadecyl side-chain was found to afford the highest yield in each of the NHC families (Scheme 60).[168,169] Other NHC ligands, as NHC-**88**, **89**, and **90** were active but not as efficient as **NHC**-**79**.

Scheme 60. Gold-catalysed phenol synthesis with complexes bearing unsymmetrically substituted NHC ligands. Reaction yield between brackets. a) reaction conditions: 0.01 mol% [Au], 3 days.[168]

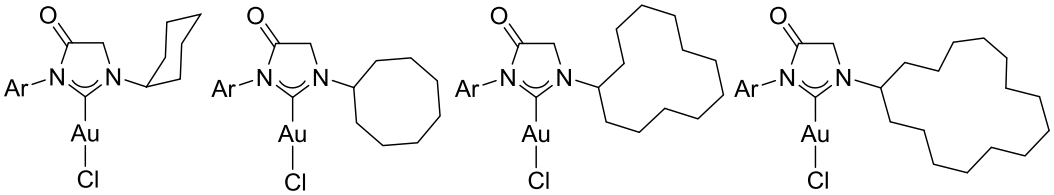




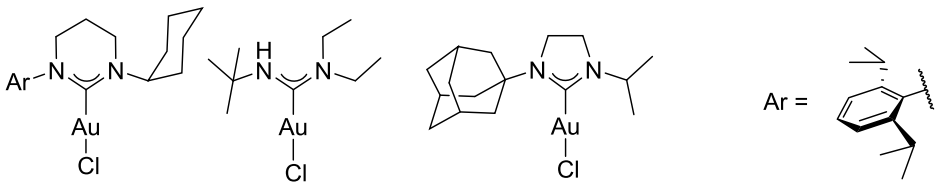
[Au(NHC-76)Cl] (68%) **[Au(NHC-77)Cl]** (62%) **[Au(NHC-78)Cl]** (66%) **[Au(NHC-79)Cl]** (90%)



[Au(NHC-80)Cl] (37%) **[Au(NHC-81)Cl]** (46%) **[Au(NHC-82)Cl]** (32%) **[Au(NHC-83)Cl]** (76%)



[Au(NHC-84)Cl] (32%) **[Au(NHC-85)Cl]** (28%) **[Au(NHC-86)Cl]** (28%) **[Au(NHC-87)Cl]** (46%)

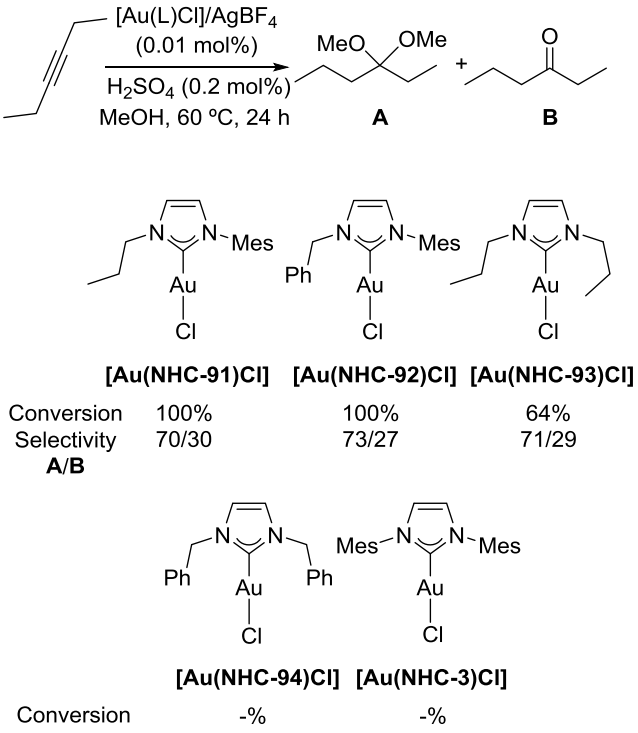


[Au(NHC-88)Cl] (48%) **[Au(NHC-89)Cl]** (68%) **[Au(NHC-90)Cl]** (55%)[a]

The different behaviour of symmetric and unsymmetric NHC-gold complexes in the alkoxylation of internal alkynes has been explored by Thieuleux and co-workers.[170] Complexes containing unsymmetrically substituted *N*-alkyl, *N*-aryl NHC ligands ([Au(**NHC-91**)Cl] and [Au(**NHC-92**)Cl]) were found to be much more efficient than the corresponding symmetrically substituted species: ([Au(**NHC-**

93)Cl], ([Au(**NHC-94**)Cl] and [Au(**NHC-3**)Cl]) which afforded moderate conversion or no reaction at all (Scheme 61).[170]

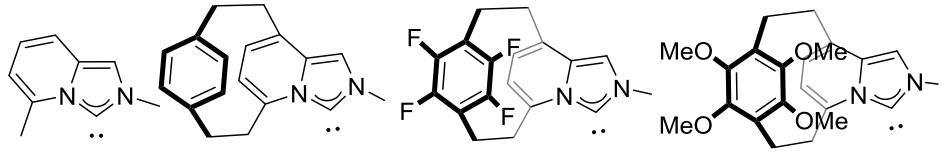
Scheme 61. Unsymetrically substituted NHC ligands employed in the alkyne alkoxylation.



3.1.8 IPy-derivatives

Imidazo[1,5-a]pyridin-3-ylidene (IPy) derivatives have been used mostly for enantioselective catalysis,[171-173] which is outwith the scope of this review. In this section we will focus on the studies dealing with IPy ligands and their role in achiral transformations.

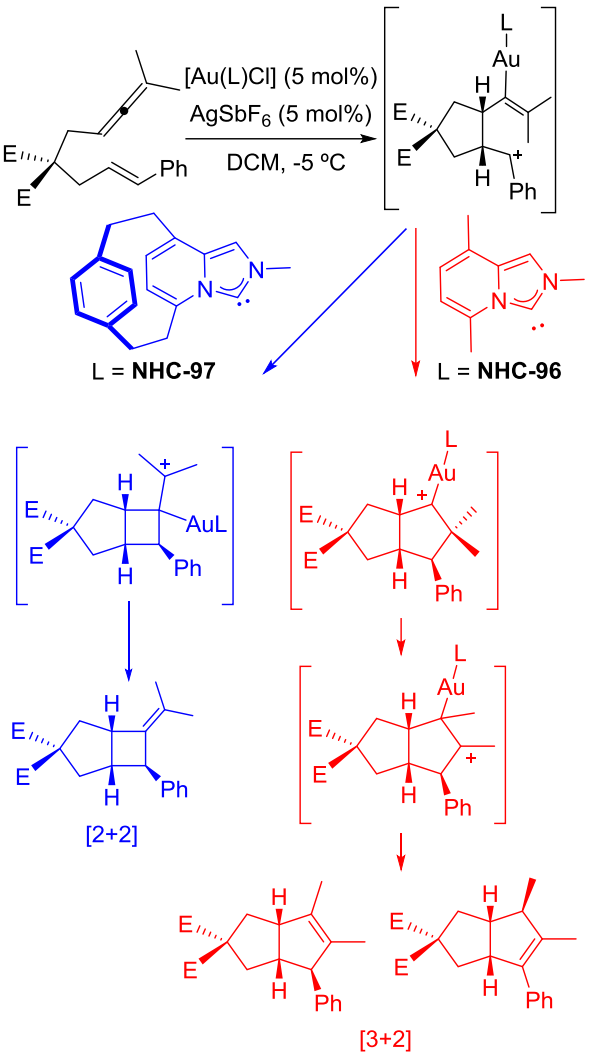
As already discussed, NHC ligands are not only σ-donor but also π-acceptor ligands. While most of the reports where the electronic properties of the NHC ligands are modulated focus on the σ-donating component, Fürstner and co-workers have shown that tuning the π-accepting properties of the carbenes can dominate the outcome of some gold(NHC)-catalysed transformations.[174] The study included imidazopyridine-2-ylidene (e.g. **NHC-95**,**96**) ligands and their cyclophanic analogues (**NHC-97**-**99**).[174] DFT calculations of the orbitals energies of these ligands allowed the analysis of their electronic properties by separating their σ-donating and π-accepting components. (Figure 25).[174] While the E_σ value (energy of the carbene lone pair orbital) of **NHC-95** and **NHC-97** are very close, the E_π (energy of the π-acceptor orbital) of the cyclophanic carbene is much lower, suggesting an increased π-accepting ability. The π-acceptor properties of the cyclophanic ligands can be easily tuned by substituting the aromatic ring (**NHC-97-99**, Figure 25).



	NHC-95	NHC-97	NHC-98	NHC-99
E_σ/eV	-4.97	-5.00	-5.14	-4.86
E_π/eV	-0.63	-1.14	-1.34	-0.85

Figure 25. Calculated carbene lone-pair orbital (E_σ) and π-acceptor orbital (E_π) energies for IPy-ligands.

To evaluate the influence of the π-acceptor properties of the NHC ligands in gold catalysis, [Au(NHC)Cl] (**NHC-96**, and **NHC-97**) species were prepared and evaluated in the cycloisomerisation of allenenes, a reaction which the outcome depends on the electronic properties of the catalyst.[174] The reaction exclusively afforded the [2+2] cycloadduct when the strong π-acceptor **NHC-97** ligand was employed. In contrast, complete selectivity for the formation of the [3+2] cycloadducts was obtained when **NHC-96** was used (Scheme 62). The different π-acceptor properties of these ligands were also evaluated in other transformations such as the intramolecular cyclisation of allene-dienes or enynes. In all cases, different products were obtained according to the different π-acidity of the ligands employed.



Scheme 62. Gold-NHC promoted [2+2] vs [3+2] enyne cycloaddition controled by the π-acidity of the ligands.

L-shaped IPy-based carbenes (**NHC-100**-**102**), which are reminiscent of Buchwald-type phosphines due to their geometry, were shown to be very efficient ligands in several gold-catalysed transformations (Figure 26).[175] The catalytic activity of the [Au(NHC)Cl] complexes containing **NHC-100**, **101**, and **102** was evaluated in several challenging transformations. **NHC-101** was found to be the most effective ligand of the family in all cases.[175] [Au(**NHC-101**)Cl], in combination with $NaBAr^F_4$, efficiently promoted the intermolecular hydroamination of terminal alkynes with anilines, affording high TON values for a Au-NHC complex (7600 TON) comparable to Buchwald-type phosphine systems and only recently surpassed by BiCAAC (Bicyclic (aryl)(amino)carbenes) (TON = 18700, see section 3.4).[176] Au-(**NHC-101**) systems catalysed challenging intermolecular additions of carboxylic acids in which [Au(**NHC-11**)NTf_2] was found to be inactive.[175] Additionally, [Au(**NHC-101**)Cl], in the presence of AgOTf, promoted the domino cyclisation/nucleophilic addition of 1,6-enynes with nucleophiles affording higher yield, TON and TOF values than [Au(**NHC-1**)Cl] and [Au(**NHC-3**)Cl], under the same conditions.[175]

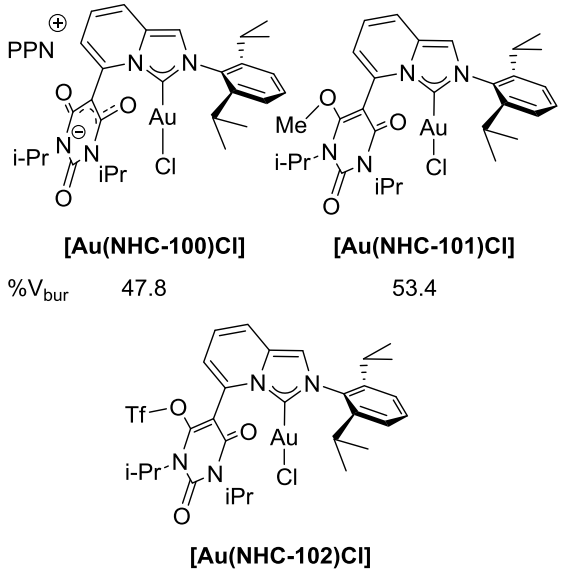


Figure 26. Gold complexes containing L-shaped NHC ligands. PPN = bis(triphenylphosphine)iminium

3.2 Expanded-ring NHC ligands

Expanded-ring NHCs (erNHC) are based on 6-10-membered ring heterocycles (Figure 27). erNHC are more donating and bulkier than the corresponding 5-ring NHC analogues. The wider N-C-N angle in erNHC results in a higher impact of the steric bulk into the metal centre.[177] Transformations where erNHC ligands have been used in gold-catalysed transformations are described in this section.

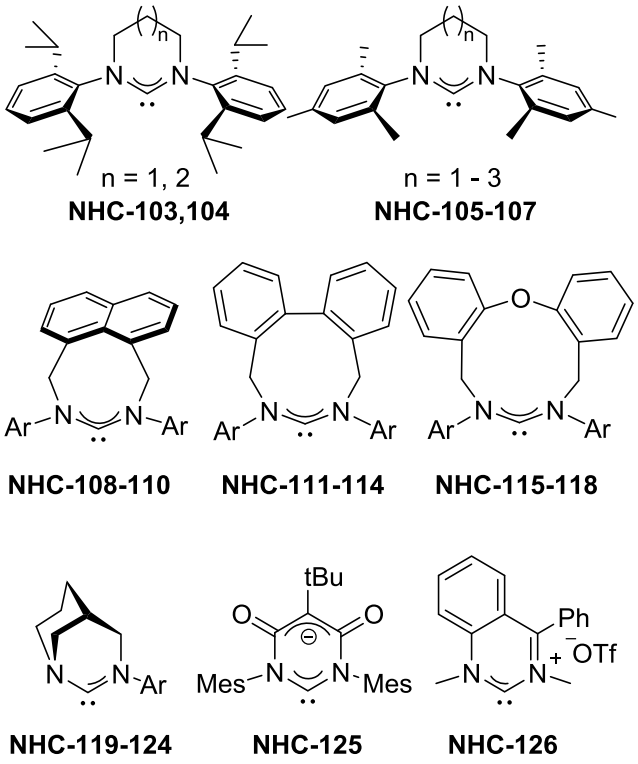


Figure 27. erNHC discussed in this section

Gold complexes containing the 6-and 7-membered ring NHC analogous of IPr (**NHC-103**[178], **NHC-104**)[179] and 6-, 7- and 8-membered ring IMes congeners (**NHC-105**-**107**)[179,180] have been synthesised and employed as pre-catalysts in some transformations. The steric hindrance of these NHCs increases with the ring size, as shown in Figure 28. This effect is more noticeable from the 5- to 6-membered ring carbenes. It should be noted that the %V_{bur} of **NHC-107** was reported using [Au(**NHC-107**)Br] and, although the same trend is obtained, comparisons should always be made between the same type of complexes (**NHC-106**: %V_{bur} = 43.1 calculated from [Au(**NHC-106**)Br][177]; and 42.9 from [Au(**NHC-106**)Cl][30]).

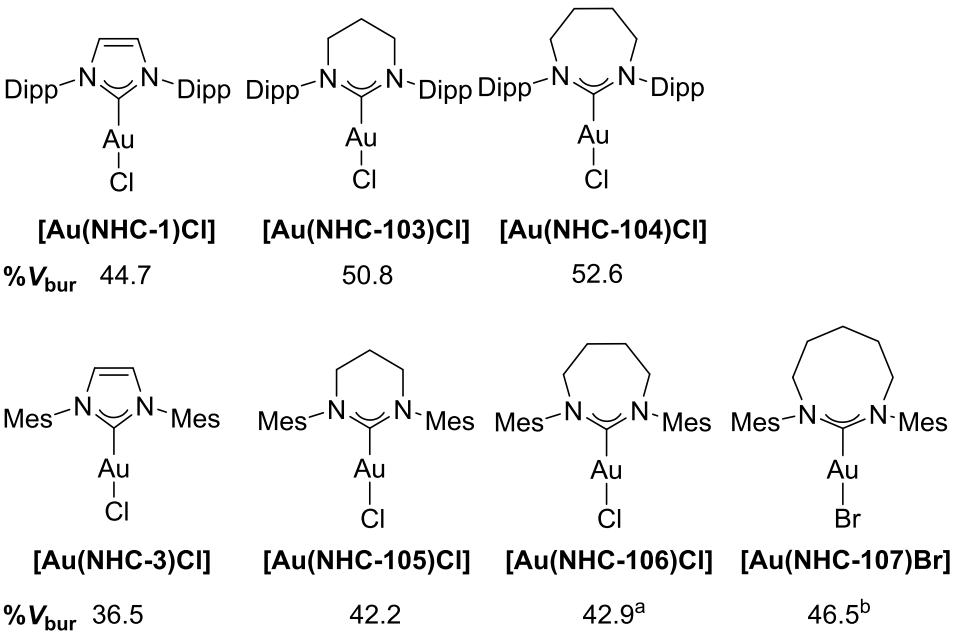
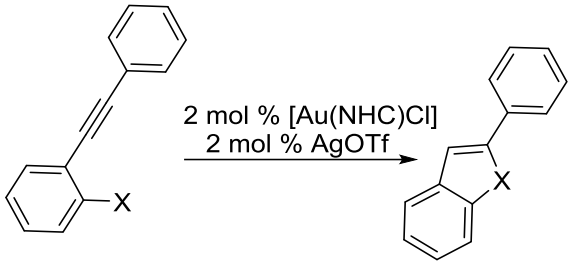


Figure 28. Au complexes containing 6-, 7- and 8-membered ring NHC ligands. $\%V_{bur}$ obtained from reference [179] and references therein, SambVca parameters: 3.50 Å sphere radius, 2.00 Å metal−ligand bond distance, hydrogen atoms were omitted, Bondi radii scaled by 1.17. a) Value obtained from reference [30] b) $\%V_{bur}$ calculated from the [Au(NHC)Br] complex. See text.[180]

Initial catalytic studies were carried out with the gold species bearing the 6-, and 7-membered ring NHCs (**NHC-103**-**106**). These complexes, in the presence of silver salts, catalysed the hydration of internal alkynes, such as 4-octyne and 2-hexyne, but were inactive with diphenylacetylene or phenylacetylene.[179]

These erNHC ligands have been also tested as ancillary ligands in the gold-promoted intramolecular heterocyclisation of 2-(phenylethynyl)aniline, *N*-methyl-2-(phenylethynyl)aniline and 2-(phenylethynyl)phenol to afford indoles and benzofuran.[181] The results obtained with the erNHC ligands (**NHC-103**-**106**) were compared to the corresponding 5-membered ring systems (IPr, SIPr, IMes, and SIMes) (Table 5). Although the results were substrate-dependent, some trends can be drawn from this study. Faster reactions were obtained with the [Au(erNHC)Cl]/AgOTf systems (Table 5) and, in contrast to the 5-membered ring NHC derivatives, catalyst decomposition was not observed after reaching completion. Bulkier erNHC containing diisopropylphenyl groups (**NHC-103**,**104**) were more active than the mesityl (**NHC-105**,**106**) derivatives, and amongst them, the 7-membered ring NHCs afforded better results (Table 5). The increased activity and stability of [Au(erNHC)Cl] complexes was attributed to the formation of stronger Au-erNHC bonds and to a higher steric stabilisation with these systems.[181] Using [Au(**NHC-104**)OTf] as the catalyst, the authors reported the intermolecular addition of Ts- and Boc-hydrazine to arylalkynes.[182]

Table 5. Ligand effect on gold promoted heterocyclisation reactions.

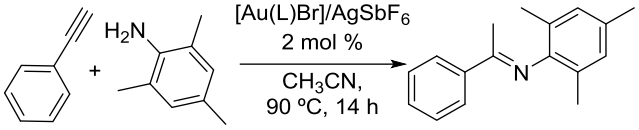


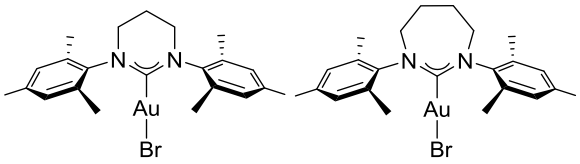
X = NH, NMe, O

		Total conversion time (min)		
Entry	**NHC**	**X = NH**	**X = NMe**	**X = O**
1	**NHC-1**	134	20	15
2	**NHC-2**	50	10	8
3	**NHC-103**	18	11	9
4	**NHC-104**	15	8	6
5	**NHC-3**	250	25	350
6	**NHC-4**	660	60	400
7	**NHC-105**	137	12	18
8	**NHC-106**	137	10	8

The catalytic activity of [Au(**NHC-107**)Br] in the intermolecular hydroamination of a terminal alkyne was studied and compared to that of the 6-, and 7-membered ring NHC-gold analogues (**NHC-105** and **106**, respectively). The three complexes afforded very good conversions, with the complex containing the larger ring size-NHC complex, [Au(**NHC-107**)Br], giving the best result (Scheme 63).[180] Additionally, [Au^{III}(erNHC)Br_3] and heterobis(er-NHC)($^{i}Pr_2$-bimy)-Au(I) and Au(III) species were prepared (bimy = benzimidazolin-2-ylidene). The former were found to be active in the transformation (74-90% yield), although they were less active than the Au(I) analogues, while the latter were inactive.[180]

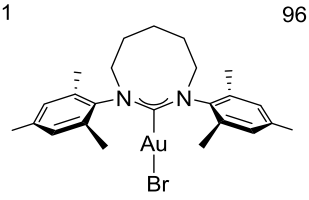
Scheme 63. erNHC ligand effect in the gold catalysed hydroamination of terminal alkynes.





[Au(NHC-105)Br] **[Au(NHC-106)Br]**

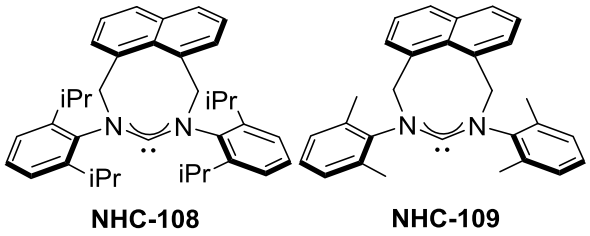
GC conversion	91	96



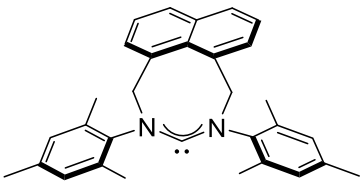
[Au(NHC-107)Br]

GC conversion (Isolated yield)	98 (94)

Hashmi and co-workers also reported the synthesis of other 8-membered ring NHC ligands (**NHC-108-110,** Figure 29), and used them as ligands in the gold-promoted cycloisomerisation of enynes and other transformations.[183] All of the gold complexes were found to be efficient pre-catalysts for enyne cycloisomerisation but showed different selectivities. For example, in the cycloisomerisation of 1,6-enynes, the *endo*-cycloadducts were predominantly obtained with **NHC-108**, while **NHC-110** favoured the formation of *exo*-products.[183]



NHC-108 **NHC-109**



NHC-110

Figure 29. 8-membered ring NHC ligands.

The same group reported the synthesis of 9-, and 10-membered ring NHC ligands with different *N*-aromatic substituents and their corresponding [Au(erNHC)Cl] complexes (9er: **NHCs**-**111**-**114**; 10er: **NHCs-115**-**118**; Figure 30). [184]

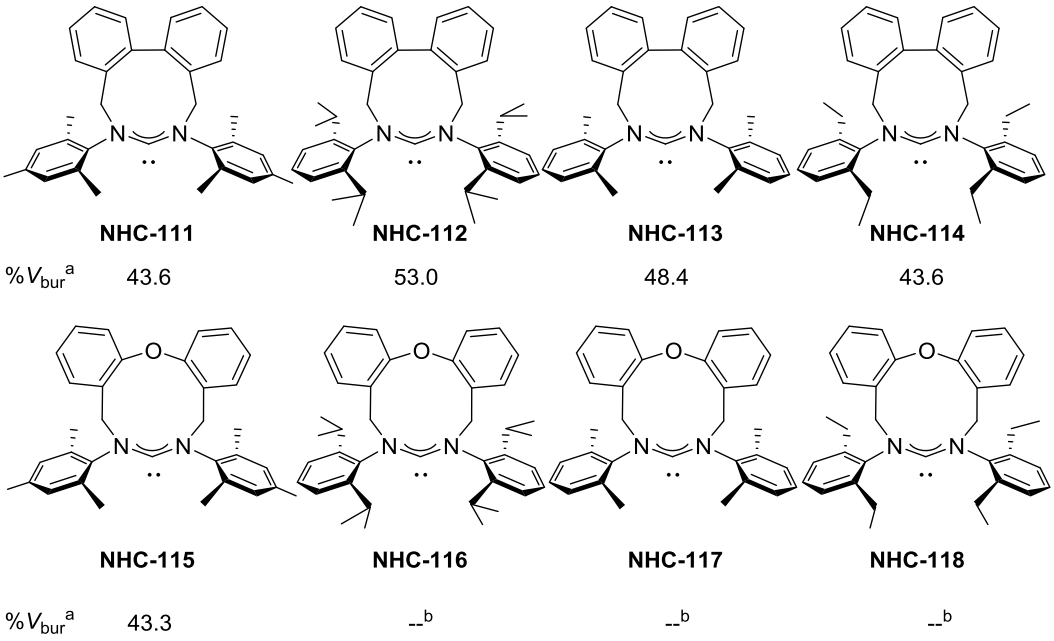
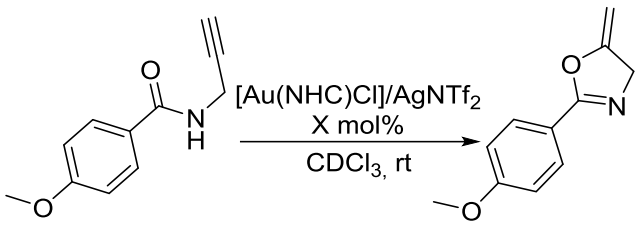


Figure 30. 9- and 10-membered ring NHC ligands. a) %V_{bur} obtained from reference [184]. Parameters for SambVca 2.0 calculations: r=3.5 a, d=2.0 a,mesh spacing=0.10, bondradii scaled by 1.17 and hydrogenatoms were omitted. b) %V_{bur} not reported.

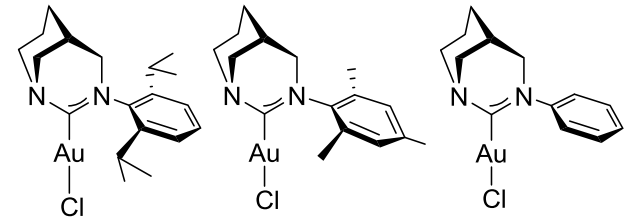
The [Au(erNHC)Cl] complexes (NHCs **111**-**118**) were used as pre-catalysts in the cycloisomerisation of a propargylamide to generate an oxazoline at room temperature with low catalyst loading (1.0-0.1 mol%). Upon activation with $AgNTf_2$, complex [Au(**NHC-111**)Cl] was found to be the most active catalyst of the series (Table 6, entry 1), followed by [Au(**NHC-115**)Cl] (Table 6, entry 5). The least active complexes were those with *N*-diisopropylphenyl substituted NHC ligands: [Au(**NHC-112**)Cl] and [Au(**NHC-116**)Cl] (Table 6, entries 2 and 6). To rationalise this behaviour, the authors studied the ligand steric distribution calculating the corresponding steric maps. The steric hindrance of the *N*-mesityl derivatives is more homogeneously distributed around the metal centre than the *N*-diisopropylphenyl steric volume. In the latter, only two isopropyl groups seem to point to the metal centre, creating two bulkier quadrants. The difference steric distribution was suggested to be the reason behind the observed catalytic activity.[184]

Table 6. Au-erNHC catalysed cycloisomerisation of propargylamide.

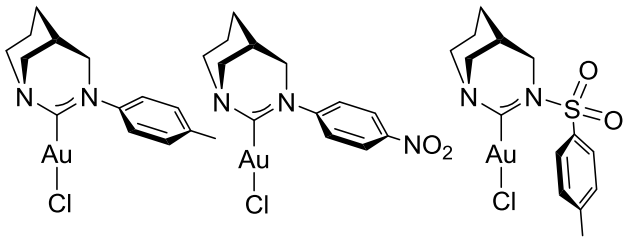


entry	NHC	NMR yield (%)	
		1.0 mol% **24 h**	**0.1 mol%** **48 h**
1	**111**	100	82
2	**112**	50	(92, 5 d)
3	**113**	99	33
4	**114**	100	(20, 6 d)
5	**115**	100	69
6	**116**	44	31
7	**117**	99	51
8	**118**	90	50

Bertrand and co-workers reported the synthesis of gold complexes containing anti-Bredt-NHC or pyrNHC ligands.[185,186] Anti-Bredt-NHCs are strong σ-donor ligands with stronger π-accepting properties than classical NHCs since one of the N atoms of the heterocycle is placed in a strained bridgehead position and cannot donate its lone pair (Figure 31).[187] Although structurally related to expanded ring-diaminocarbenes, the electronic properties of Anti-Bredt NHCs resemble those of cyclic (aryl)amino carbenes (CAACs, see section 3.4).[188] Since CAACs have been demonstrated to be highly efficient ligands for gold-catalysed hydroamination and hydrohydrazination reactions,[188,189] anti-Bredt NHCs have been tested in these transformations.



[Au(NHC-119)Cl] **[Au(NHC-120)Cl]** **[Au(NHC-121)Cl]**

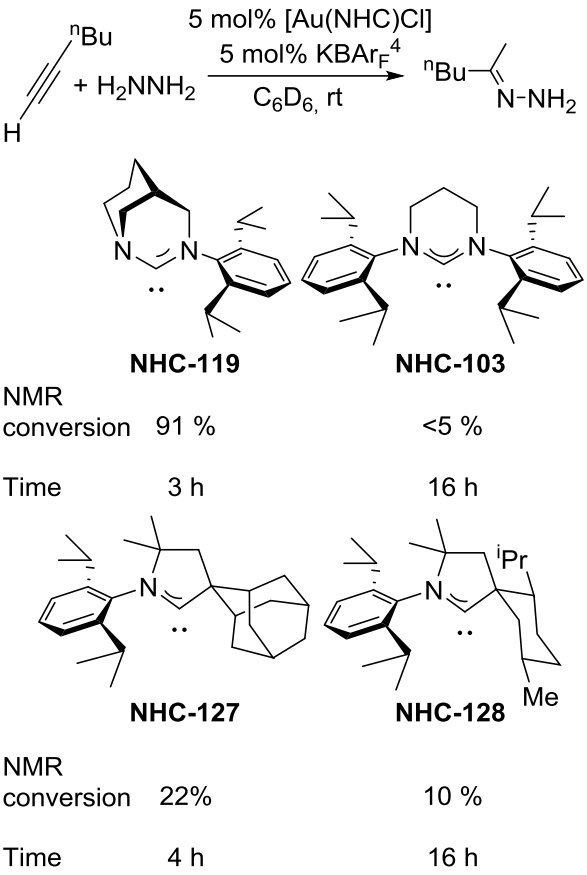


[Au(NHC-122)Cl] **[Au(NHC-123)Cl]** **[Au(NHC-124)Cl]**

Figure 31. [Au(pyr-NHC)Cl] complexes used in catalysis

Remarkably, the Au-(**NHC-119**) system efficiently catalysed the hydrazination of 1-hexyne at room temperature. Very low yields were obtained with the structurally related er-NHC (**NHC-103**) and CAAC ligands, **NHC-127** and **128**, under the same conditions. The Au-**NHC-127** and **128** catalysts required high temperatures (70-110 ºC) to afford the product in high yields (Scheme 64).[185] The Au-(**NHC-119**)Cl/$KBAr_F^4$ catalytic system promoted the formation of different hydrazones. However, to achieve full conversion with bulkier (e.g. tert-butyl acetylene) or electron poor alkynes (e.g. phenylacetylene, Scheme 68), heating at 75-110 ºC was required.

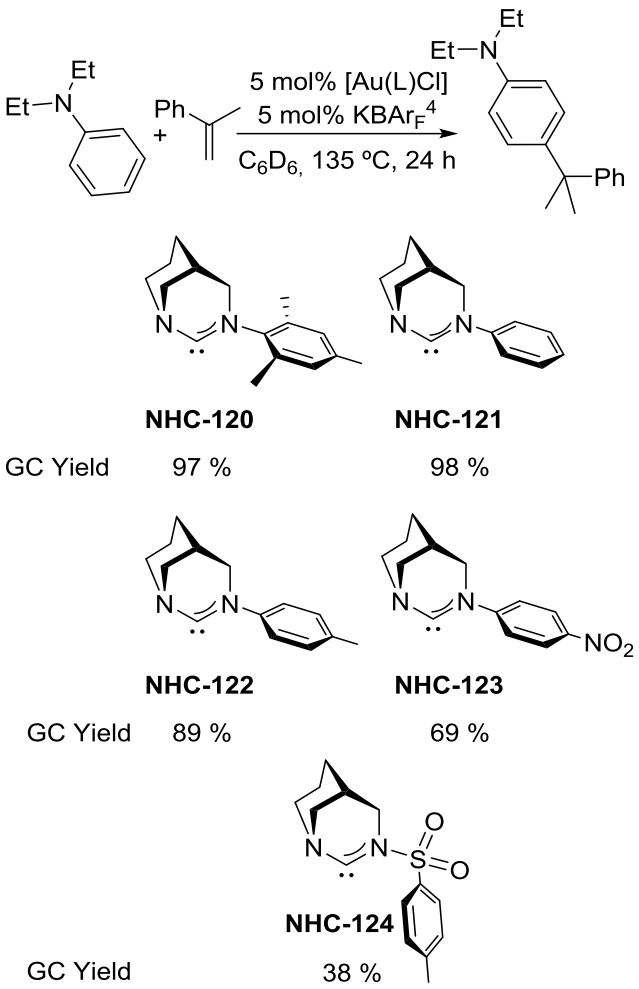
Scheme 64. Room-temperature hydrohydrazination of 1-hexyne with Au-antiBredt NHC complexes.



The effect of the *N*-substitution in anti-Bredt ligands has been evaluated.[186,190] Gold complexes containing **NHCs-120**-**122** and **124** promoted the hydroamination of phenylacetylene with aniline at room temperature. However, the ligand structure did not affect the reaction outcome since all of the complexes tested gave the same kinetic profile.[190]

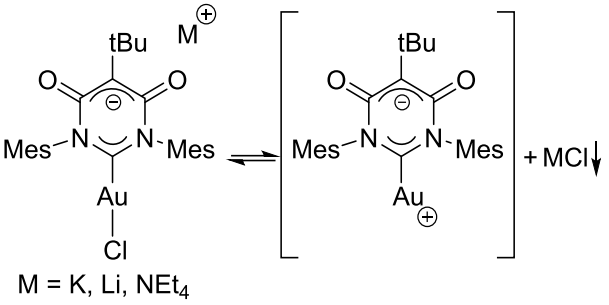
Au(pyr) species (**NHC-120**-**124**) allowed for the development of the hydroarylation of alkenes (styrenes, norbornene, and enones) with *N*,*N*-dialkylanilines with high *para*-selectivity (Scheme 65).[186] The high selectivity was associated with the steric hindrance of the *N*-aryl substituent. In this reaction, **NHC-120**-**122** were the most efficient ligands of the family, affording comparable yields. The gold complex containing the ligand with a *p*-NO_2 group (**NHC-123**) gave the product in lower yields, and the yield obtained with the Au-(**NHC-124**) system stalled at 38%, suggesting catalyst decomposition.[186] This transformation was further improved with CAAC ligands, which afforded high yields in shorter reaction times and employing 1 mol% of catalyst loading (section 3.4, Scheme 71). [191]

Scheme 65. Au(pyr)-promoted hydroarylation of alkenes with anilines.



Anionic expanded-ring NHC species have been synthesised and coordinated to gold affording ionic complexes. These poorly soluble species, [Au(**NHC-125**)Cl]M (Scheme 66), were postulated to slowly release soluble zwitterionic catalytically active gold fragments into the solution. These species were found to be active in the cycloisomerisation of 1,6-enynes without the need for activation. [Au(IPr)Cl] and [Au(**NHC-105**)Cl] were also tested and did not afford any product under the same reaction conditions.[192]

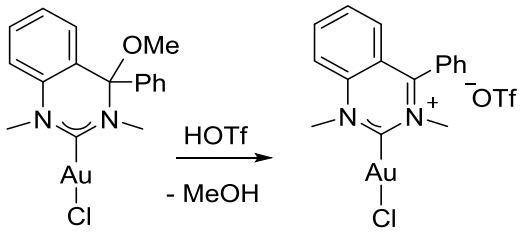
Scheme 66. Proposed equilibrium between the insoluble [Au(**NHC-125**)Cl]M species and the zwitterionic catalytically active form.



[Au(NHC-125)Cl]M **[Au(NHC-125)]**

Ganter and co-workers prepared a gold complex containing a cationic 6-membered ring NHC with a quinazolinium structure (**NHC-126**) by treatment of the corresponding neutral species, [Au(**NHC-129**)Cl], with HOTf (Scheme 67).[193] The cationic **NHC-126** ligand was found to be significantly less donating and a much better π-acceptor (TEP = 2073 cm^{-1}, δ(^{77}Se) = 768 ppm) than the neutral **NHC-129** carbene (TEP = 2054 cm^{-1}, δ(^{77}Se) = 361 ppm). The gold-catalysed cyclisation of a propargylamide was chosen to evaluate the ligand effect. The reaction was carried out in acetonitrile, at room temperature, using 5 mol% of the Au-NHC (**NHC-126**,**129**) complexes and 5 mol% of AgOTf. The activity of the cationic species was higher (62 and 99 % yield after 1, and 7 h, respectively) than that of the neutral complex (18 and 62 % yield after 1 and 7 h, respectively).[193]

Scheme 67. Quinazolinium-based expanded-ring NHC-Au complexes employed in catalysis.

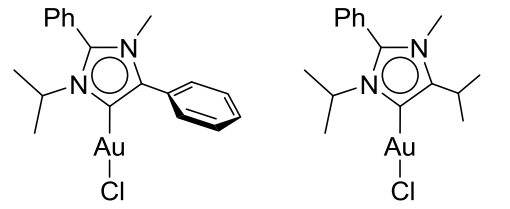


[Au(NHC-129)Cl] **[Au(NHC-126)Cl]OTf**

3.3 Abnormal imidazol(id)inylidene ligands

"Abnormal" or mesoinic carbenes are a family of NHCs that cannot be represented by a neutral uncharged covalent structure. "Abnormal" imidazolylidene ligands (aNHC) coordinate to the metal centre through the C4 or C5 position and they are more electron-donating than the "normal" C2 analogues.[194,195]

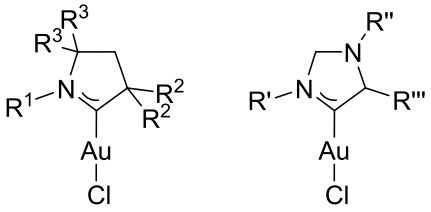
Gold complexes containing abnormal imidazolin-5-ylidine ligands ([Au(**NHC-130**,**131**)Cl]) have been prepared (Figure 32). These complexes were tested in the hydration of phenylacetylene, showing worse catalytic activity than that of the analogous C2-bonded NHC species.[196]



[Au(NHC-130)Cl] **[Au(NHC-131)Cl]**

Figure 32. Au complexes containing aNHC ligands used in alkyne hydration.

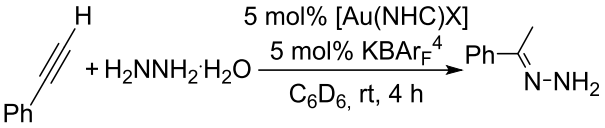
Hashmi reported the synthesis of a range of gold complexes containing saturated abnormal NHC carbenes (saNHC) via 1,3-dipolar cycloadditions on isocyanide gold complexes.[197] Au-saNHC species proved active in challenging furan-yne reations with moderate TON values.[197] Due to the similarities to CAACs (Figure 33), the ability of Au-saNHC (**NHC-132**,**133**) complexes to promote the hydrohydrazination of alkynes (see sections 3.2 and 3.4), was further explored (Scheme 68).[198]

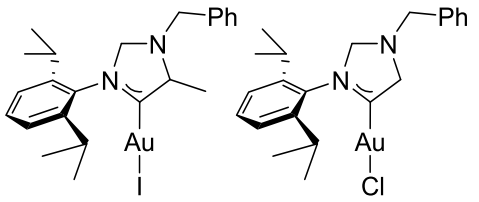


[Au(CAAC)Cl] **[Au(saNHC)Cl]**

Figure 33. Structurally related CAAC- and saNHC-gold complexes

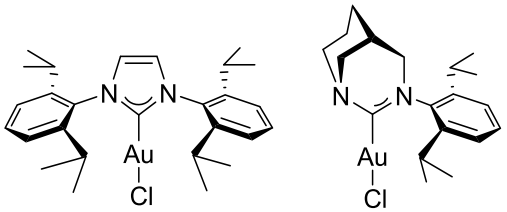
Scheme 68. Au-saNHC compelxes as catalyts for the hydrohydrazination of phenylacetylene. a) see reference [185].





[Au(NHC-132)I] **[Au(NHC-133)Cl]**

NMR Yield 92% 22%



[Au(NHC-1)Cl] **[Au(NHC-119)Cl]**

NMR Yield 65% -%

(87%, 90 ºC)[a]

[Au(**NHC-132**)I], containing a saNHC ligand, was found to efficiently promote the hydroamination of phenylacetylene with hydrazine at room temperature (Scheme 68).[198] The substitution on the C5 position played an important role, and complex [Au(**NHC-133**)Cl] afforded the hydrohydrazination product in poor yield (Scheme 68).[198] The complex bearing an anti-Bredt ligand, [Au(**NHC-119**)Cl], was only able to promote this transformation at 90 ºC. However, when using 1-hexyne, [Au(**NHC-119**)Cl] was more efficient than[Au(**NHC-132**)I] (91 % yield after 3 h vs 51% yield after 4 h, respectively; see section 3.2).[185] The reaction mechanism and comparison between CAAC, anti-Bredt, and saNHC ligands has been studied by means of DFT calculations.[199] This study shows that the barrier for the rate limiting step is similar for Au-CAACs and Au-anti-Bredt complexes; and slightly lower for Au-saNHC species.[199]

3.4 Cyclic (alkyl)(amino)carbenes

Cyclic (alkyl)(amino)carbenes (CAACs) are a variation of classical NHCs where one of the N atoms of the heterocycle has been replaced by a quaternary carbon atom. As a consequence of this structural modification, CAACs are both stronger σ-donors and stronger π-acceptors than classical diaminocarbenes.[188,200] The CAAC structure has also been modified to tune the carbene properties. The most relevant members of the CAAC family employed as ligands in gold catalysis are:

cyclic(amino)(aryl) carbenes (CAArC);[201] expanded-ring CAACs (CAAC-6);[202] and bicyclic (alkyl)(amino)carbenes (BiCAAC)[203] (Figure 34).

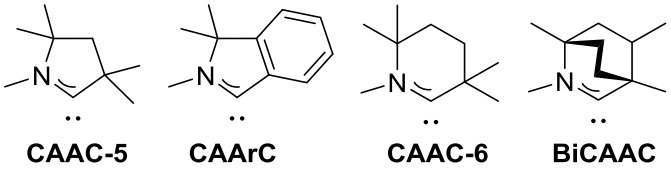


Figure 34. Representative examples of CAAC ligands and related carbenes.

As expected, the steric and electronic properties of the CAACs depend on their core structure. As mentioned before, CAAC-5 are both more σ-donating and more π-accepting than classical NHCs. BICAACs, with a biclyclic core structure are more ambiphilic than CAACs and their steric properties resemble that of the classical NHCs.[203] Finally, the CAAC-6 structures are the best σ-donors and π-acceptors of these series (Figure 35).[202] CAAC-6 structures showed a wider N-C-C angle and are, therefore, more sterically hindered than the corresponding CAAC-5 derivatives, as occurs with the diaminocarbenes previously discussed (section 3.2).[189]

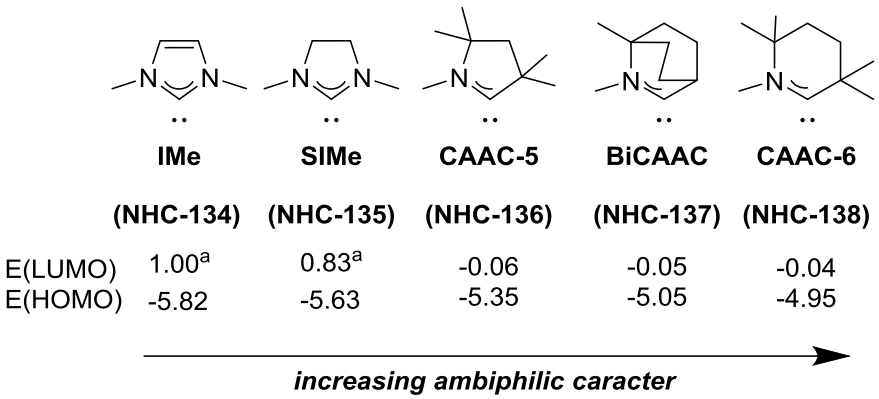


Figure 35. Reported calculated HOMO and LUMO energies of different NHC carbenes relevant to gold catalysis (B3LYP/ def2-TZVPP level of theory with ultrafine grid). a) LUMO+1. Adapted from reference [189]

A comprehensive review on the coordination chemistry of CAACs to coinage metals and their applications has been recently published, including the most relevant catalytic processes developed with Au-CAAC complexes.[189] In this section we will briefly discuss the catalytic applications of these complexes and will focus on those reports where the ligand effect has been explored.

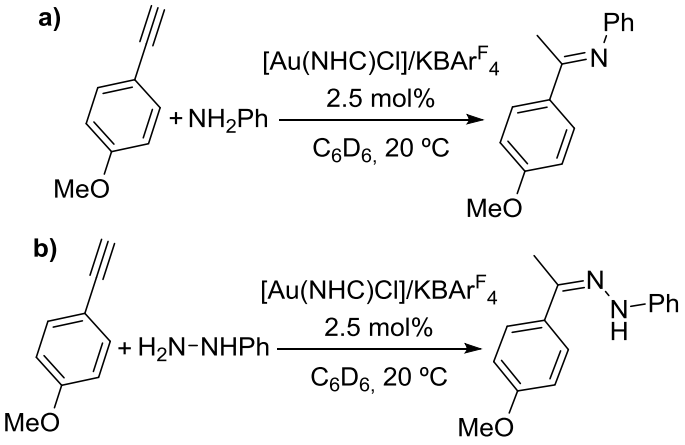
The use of CAAC ligands in gold catalysis has allowed for the development of new and challenging transformations.[204-206] CAACs have demonstrated to be remarkable ligands in hydroamination and hydrohydrazination of alkynes.[189] For example, [Au(**NHC-127**)Cl]/KB(C_6F_5)$_4$, [Au(**NHC-127**)(toluene)]$^+$ or [Au(**NHC-127**)(NH_3)]$^+$ were the first homogeneous catalysts to promote hydroamination of alkynes and allenes with NH_3[207] and hydrazine.[208] They have been used to synthesise allenes from cross-

coupling reactions between terminal alkynes and enamines; [204] and from alkynes and a sacrificial amine in a one-pot protocol.[205]

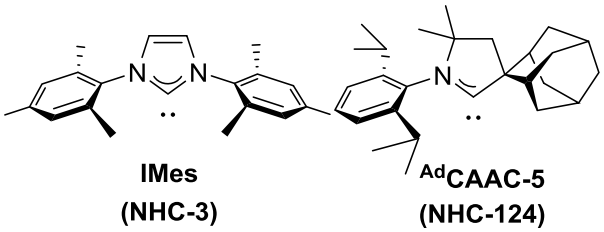
Particularly relevant to this review is the thorough study on the ligand effect of gold-catalysed hydroamination and hydrohydrazination of alkynes reported by Bertrand and co-workers.[176] The activity of gold complexes containing PPh_3, IMes (**NHC-3**), and cyclic(alkyl)(amino) carbenes was evaluated.[176] To determine the effect of the CAACs structure on reactivity, several structures were studied, including: 5-membered ring NHCs ^{Ad}CAAC-5 (**NHC-127**) and ^{Et}CAAC-5 (**NHC-136**); 6-membered ring NHC ^{Et}CAAC-6 (**NHC-140**); and bicyclic (alkyl)(amino)carbenes ^{IPr}BiCAAC (**NHC-141**) and ^{Me}BiCAAC (**NHC-142**) (Scheme 69).

Scheme 69. Ligands evaluated in the gold-catalysed hydroamination and hydrohydrazination of alkynes.

Reactions studied:



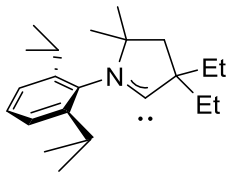
NHC ligands evaluated:



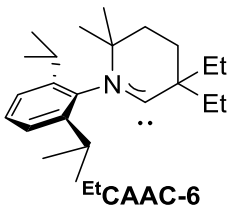
IMes
(NHC-3)

^{Ad}CAAC-5
(NHC-124)

$\%V_{bur}$ 37.5 48.4

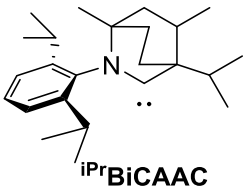


^{Et}CAAC-5
(NHC-139)

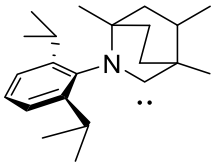


^{Et}CAAC-6
(NHC-140)

$\%V_{bur}$ 43.2 47.4



^{iPr}BiCAAC
(NHC-141)



^{Me}BiCAAC
(NHC-142)

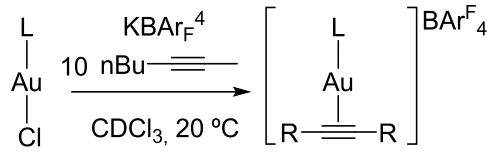
$\%V_{bur}$ 42.1-46.5

Kinetic analyses showed that all the complexes containing carbene ligands were more efficient than the Au-PPh_3 system both in the hydroamination and hydrohydrazination reactions. The ^{IPr}BiCAAC ligand (**NHC-141**) afforded the best catalyst in terms of rate and reaction yield, followed by IMes (**NHC-3**), in all cases. When using a secondary amine as nucleophile (Scheme 69, reaction **a**), the Au-CAAC-5 complexes (**NHC-127** and **136**) afforded similar results and were slightly better than the Au-CAAC-6

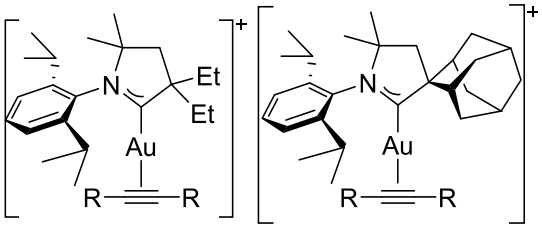
system (**NHC-140**). In the hydrohydrazination reaction, the system containing the CAAC-6 ligand (**NHC-140**) was slightly better than that bearing a CAAC-5 (**NHC-127**). In this case, the Au-CAAC-5 system (**NHC-136**), performed poorly and this was attributed to the formation of an inactive bis(NHC)-Au species in the media. Additionally, the activity of the gold derivative containing a less bulky BiCAAC ligand, ^{Me}BiCAAC (**NHC-142**), was found to be inferior to that of Au-**NHC-141**. According to these results there was not a direct correlation between catalytic activities and the electronic or steric properties as individual factors. The high catalytic activity of the Au-**NHC-141** species was proposed to be due to a combination of moderate steric bulk and significant ambiphilicty.[176]

To gain understanding of the stability of the gold catalysts employed, the authors studied the decay of the π-alkyne gold complexes generated during the catalytic cycle under pseudo-catalytic conditions.[176] The π-alkyne gold complexes containing NHCs-**127**, **136**, and **141** were found to be stable, while those bearing NHCs-**140**, **142**, or PPh_3 suffered a rapid decay (Scheme 70. Additionally, the authors performed DFT calculations to obtain the energy barrier between the corresponding Au-NH_2R complexes, or catalyst resting state, and the Au-π-alkyne complexes, finding that this barrier is lower for the complex containing the ^{IPr}BiCAAC (**NHC-141**) ligand. [176,199] ^{IPr}BiCAAC (**NHC-141**) was proposed to sterically stabilise the metal centre, preventing decomposition, favouring the formation of the active species, and lowering the barrier for proton transfer.

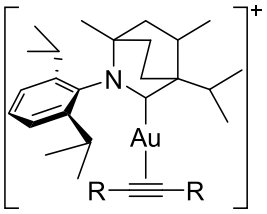
Scheme 70. Stability study of Au(NHC)-alkyne complexes.



stable species:

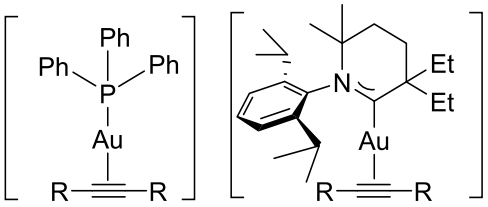


NHC-139 **NHC-127**

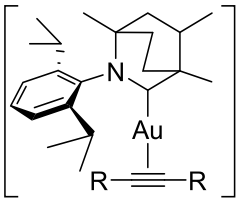


NHC-141

unstable species:



P-1 **NHC-140**



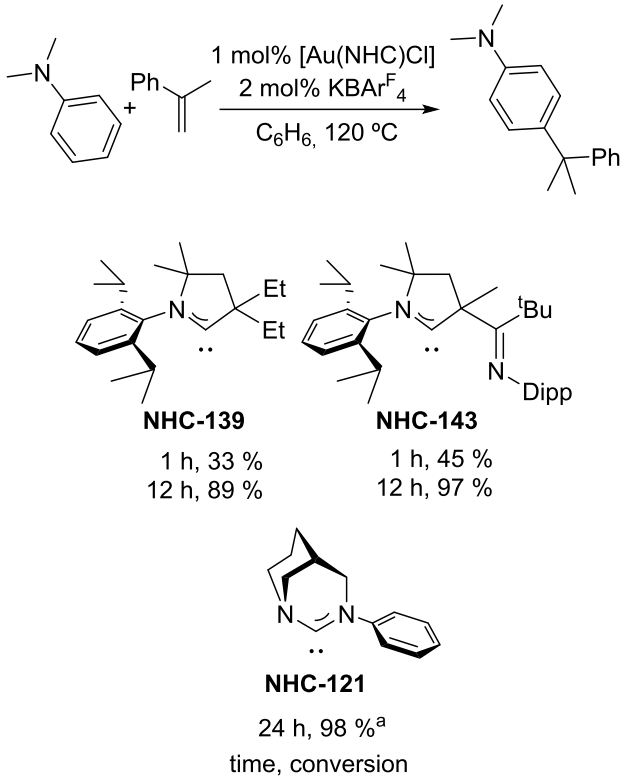
NHC-142

^{IPr}BiCAAC (**NHC-141**) was further compared to the most efficient gold-NHC and gold-phosphine catalysts reported for the hydroamination of phenylacetylene with aniline.[176] The Au-^{IPr}BiCAAC (**NHC-141**) system afforded higher TON values (0.0025 mol%, 18700 TON in 19 h at 80 ºC) than the Au-(**NHC-101**) system (0.01 mol%, 7600 TON in 37 h at 80 ºC)[175] (see section 3.1.8) and the Au-WangPhos (**P-89**) catalytic system (0.01 mol%, 8500 TON in 18 h at 80 ºC).[73] Au complexes containing anionic perhalogenatedcarborane substituted phosphines afforded a 22000 TON in 16 h at 50 ºC (0.004 mol%).[209]

3.4.1 Hemilabile Cyclic(alkyl)(Amino)carbenes

The incorporation of pendant groups to the CAAC-5 structure has been explored.[191] The presence of a basic moiety on the CAAC structure was hypothesised to assist reactions where a proton transfer was involved. To test this hypothesis, the activity of gold complexes containing the **NHC-139** and **NHC-143** ligands was evaluated in the hydroarylation of α-methylstyrene with *N,N*-dimethyl aniline (Scheme 71).[191] The Au- **NHC-143** system, containing the hemilabile CAAC ligand, was found to be more active than the Au-**NHC-139** analogue. This transformation had been previously reported using Au-anti-Bredt NHC complexes (**NHC-119-124)** complexes, although harsher reaction conditions were required (see section 3.2).[186]

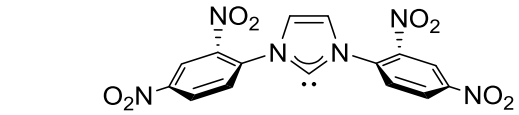
Scheme 71. Au-NHC promoted hydroarylation of α-methylstyrene with N,N-dimethyl aniline. a) Reaction conditions: 5 mol% [Au(NHC)Cl]/$KBAr^F_4$, C_6H_6, 135 ºC[186]



3.5. Triazole-based NHCs

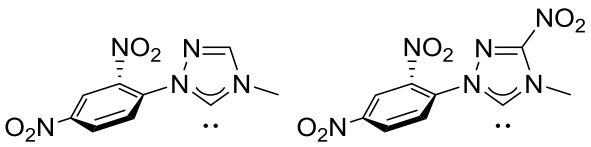
Triazole-based NHCs have been used as ligands in transition metal catalysed reactions.[210-212] These ligands have attracted attention because their structure can be easily modified, and therefore the electronic and steric properties can be easily tuned. Example of gold-triazole-based NHC complexes used in catalysis are discussed below.

Sato, Oi and co-workers described the synthesis of two gold complexes containing 1,2,4-triazol-3-ylidenes ligands (**NHC-144**, **NHC-145**).[132] These ligands were found to be poor σ-donors and strong π-acceptors (Figure 36); in fact, these were less electron-donating than the analogous imidazolin-2-ylidene, **NHC-18**, according to their TEP values.[130] With the electronic properties of the ligands in mind, the authors explored the catalytic activity of the gold complexes in the hydroalkoxylation of cyclohexene with 2-methoxyethanol and compared to that of gold derivatives containing IPr, PPh_3, $P(OPh)_3$ and **NHC-18**. As seen in section 3.1.3, electron deficient ligands favour this reaction, in agreement with the alkene electronic activation being the rate limiting step.[132,213] Accordingly, the reaction rates and yield follow an electronic trend. Complexes bearing less electron-donating ligands, **NHC-145, NHC-144**, and $P(OPh)_3$**,** were the most active in this transformation (Scheme 72).[132]



NHC-18

TEP (cm^{-1}) 2056

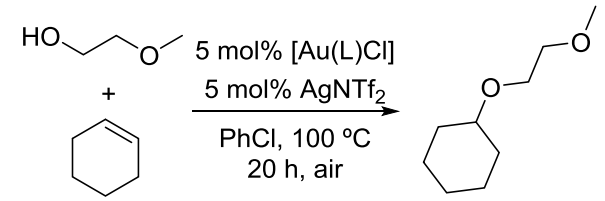


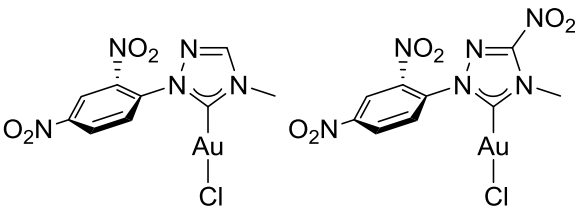
NHC-144 **NHC-145**

TEP (cm^{-1}) 2064 2069

Figure 36. Electronic properties of NO_2-containing triazole carbenes.

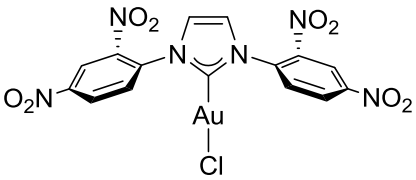
Scheme 72. Hydroarylation of cyclohexene with gold complexes containing π-accepting NHC ligands. GC yield.





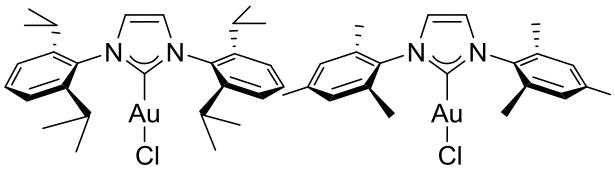
NHC-144 74 %

NHC-145 81 %



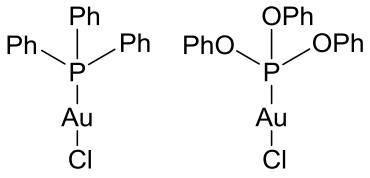
NHC-18

66 %



NHC-1 7 %

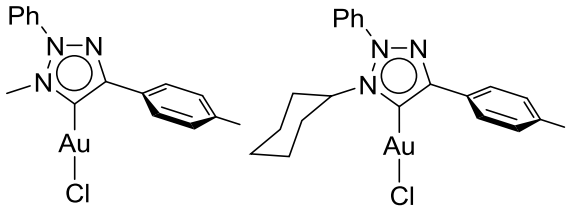
NHC-3 59 %



P-1 63 %

P-69 71 %

Although the majority of triazolylidene ligands are mesoionic structures (*vide infra*). gold complexes containing "normal" 1,2,3 triazolylidene ligands (**NHC-146**,**147**) have also been described (Figure 37).[214] The triazolylidene-gold complexes prepared were tested on the intramolecular hydroamination of alkyne-amines. These complexes were compared to the corresponding Au-IPr derivatives (**NHC-1**), the latter being slightly more effective.[214]



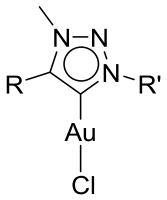
[Au(NHC-146)Cl] **[Au(NHC-147)Cl]**

Figure 37. Gold complexes bearing "normal" 1,2,3 triazolylidene ligands employed in catalysis.

3.5.1 Mesoionic Triazolylidenes

Mesoionic triazolylidenes are stronger electron donors than imidazolin-2-ylidenes but less electron donating than other mesoionic carbenes, such as 4-imidazolinylidenes.[194,212] The use of these ligands in gold catalysis is described in this section.

A family of gold complexes containing 1,2,3-triazol-5-ylidene ligands (trz) with different substituents (**NHC-148**-**153**) was prepared and their catalytic activity assessed (Figure 38).[215]

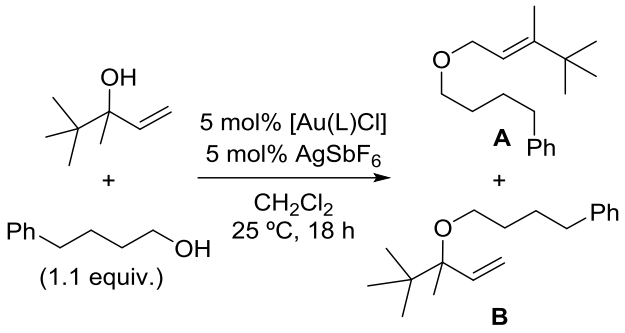


	R	R'
NHC-148	Ph	Bn
NHC-149	*p*-C_6H_4(OMe)	Bn
NHC-150	*p*-C_6H_4(NO_2)	Bn
NHC-151	Bn	Bn
NHC-152	Ph	Ph
NHC-153	Mes	Mes

Figure 38. [Au(trz)Cl] complexes in catalysis.

[Au(trz)Cl] (**NHC-148**-**153**) complexes were used as pre-catalysts for the direct etherification of allylic alcohols and compared to other gold catalysts (Table 7).[215] All of the [Au(trz)Cl] complexes (**NHC-148**-**153** afforded product **A** in high selectivity (**A**:**B** >20:1). The reaction yield seemed to be affected by the electronic properties of the trz ligand (Table 7, entries 1-3). The higher E:Z selectivity was obtained with the gold complex containing **NHC-152** (Table 7, entry 5). [Au(IMes)Cl] gave similar results to the Au-trz species, although a lower *E*:*Z* selectivity was obtained. Under the same reaction conditions, [Au(IPr)Cl] gave incomplete conversion and a lower **A**:**B** selectivity was obtained with [Au(PPh_3)Cl].[215]

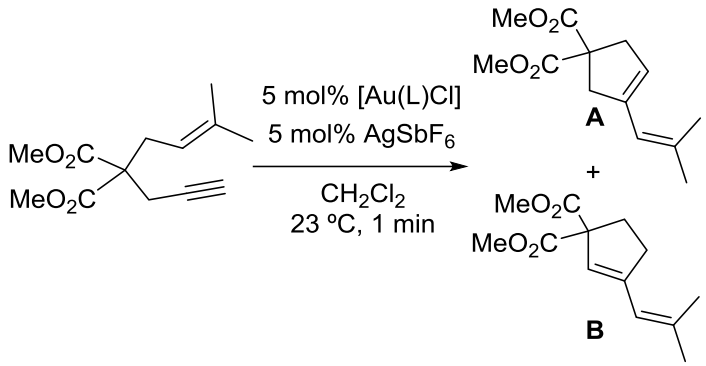
Table 7. Au(trz)-promoted direct allylic etherification. [a]Incomplete reaction



entry	NHC	A:B	Yield of A %	*E:Z*
1	**148**	>20:1	74	6:1
2	**149**	>20:1	76	8:1
3	**150**	>20:1	64	8:1
4	**151**	>20:1	67	9:1
5	**152**	>20:1	67	12:1
6	**153**	>20:1	66	6:1
7	**PPh_3**	17:1	61	4:1
8	**IPr**	2.5:1	-[a]	4:1
9	**IMes**	>20:1	70	5:1

The catalytic activity of [Au(trz)Cl] (**NHC-148**-**153**) complexes was also assessed in the cycloisomerisation of 1,6-enynes (Table 8). Selectivity to species **a** was obtained with all the complexes when the reaction was stopped after 1 min (selectivity was lost after 15 min). The different electronic nature of the R groups in the NHC ligand did not affect the reaction outcome in this case, and very similar results were obtained with complexes containing the **NHC-148**-**150** ligands (>20:1 **A**:**B** selectivity, 92-95% yield). **NHC-151** afforded a lower **A:B** selectivity (13:1), and **NHC-152**, gave high selectivity but lower yield (>20:1 **A**:**B** selectivity, 72% yield). Slightly better results were obtained with complexes containing bulky ligands (>20:1 selectivity, 98 % isolated yield), in particular with that bearing two mesityl groups, **NHC-153**. The activity of this catalyst compare to that of Au-PR_3 species (PR_3 = PPh_3 or Johnphos).[215]

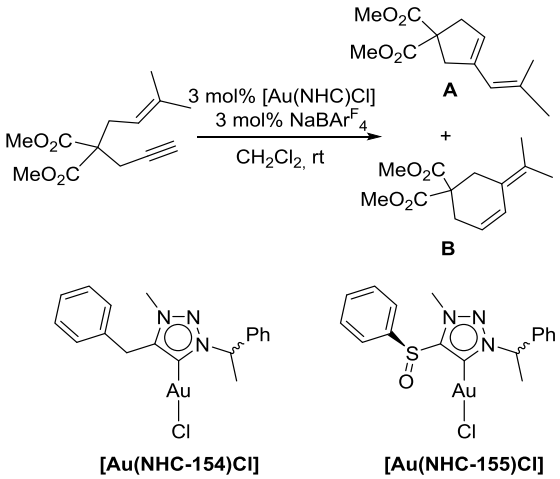
Table 8. Au(trz)-promoted enyne cycloisomerisation.



entry	NHC	A:B	Yield %
1	**148**	>20:1	92
2	**149**	20:1	94
3	**150**	>20:1	95
4	**151**	13:1	93
5	**152**	>20:1	72
6	**153**	>20:1	98

The presence of a sulfonyl moiety in the triazolylidene ligand was found to impact the outcome of enyne cycloisomerisations.[216] While [Au(trz)Cl] complexes (**NHC-154**) did not afford any cycloadduct under the conditions shown in Scheme 73, the [Au(trz)Cl] complexes containing a sulfonyl moiety (**NHC-155**) promoted the cycloisomerisation reaction, favouring the formation of product **A**.[216]

Scheme 73. Sulfonyl-containing triazolylidene ligands.

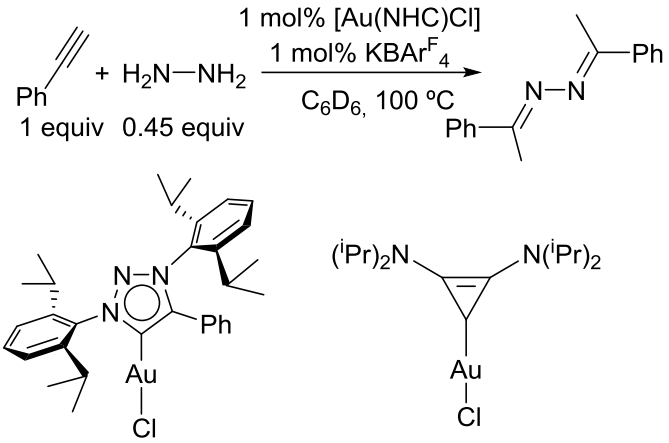


The applicability of gold-triazolylidene compounds in the oxazoline synthesis has been studied in different reports.[217-219] Initial work showed that a combination of Au-triazolylidene complexes and silver salts resulted in very efficient systems able to promote the aldol condensation of isocyanoacetate and aldehydes to give oxazolines.[217] Mechanistic studies on the systems suggested

that the catalytically active species was not a Au-triazolylidene species but ligandless gold aggregates or Ag-triazolylidine complexes. [217] These species would form in the reaction media by carbene transfer reactions mediated by the presence of silver cations. These results prompted following studies on silver-free protocols to activate Au-triazolylidene derivatives. [218,219] KPF_6, KOTf or MeOTf were successfully employed as chloride scavengers in the activation of Au-triazolylidene species but the catalytic activity was much lower than that obtained in the presence of silver salts.[219] $Cu(OTf)_2$ was also employed as a chloride scavenger in the gold-promoted synthesis of oxazolines *via* propargylamine cyclisation.[218] In this case, the catalytic system [Au(triazolylidene)Cl]/$Cu(OTf)_2$ was comparable to [Au(triazolylidene)Cl]/$AgSbF_6$, and the species containing bulkier triazolylidene ligands afforded better catalytic results. [218]

Bertrand and co-workers reported a bis-hydrohydrazination reaction of alkynes with hydrazine.[220] While gold complexes containing anti-Bredt NHC (section 3.2), saNHC (section 3.3), and CAACs (section 3.4) ligands efficiently promote the hydrohydrazination of alkynes, the use of the mesoionic ligand **NHC-156** allowed for the development of the bis-hydrohydrazination reaction of alkynes (Scheme 74). The bis(diisopropylamino)cyclopropenylidene BAC ligand (**NHC-157**, Scheme 74) was not able to promote such transformation. [220]

Scheme 74. Au-triazolylidene ctalysed bishidrohydrazination of pehnylacetylene with hydrazine.



[Au(NHC-156)]
84% azine

[Au(NHC-157)]
0% azine
(12% hydrazone)

3.6. *N*-Acyclic carbenes

N-acyclic carbenes (ADC) present a wider NCN angle than that of classical NHC ligands, which results in a higher steric impact around the metal centre. They are also more flexible than the cyclic derivatives. ADC are generally more electron donating than classical NHCs and expanded NHC ligands, and less electron donating than NHCs with reduced heteroatom stabilisation, according to their HEP values.[221] Although they are not as popular as the 'cyclic carbenes', they have also been used as ligands in gold catalysis (Figure 39).[222,223]

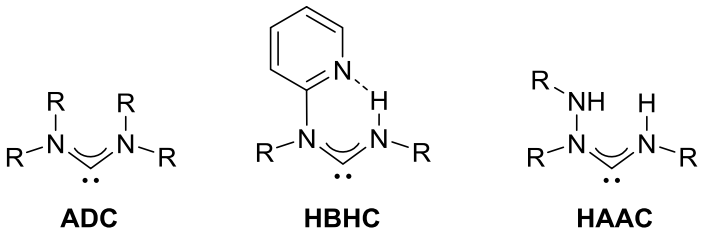
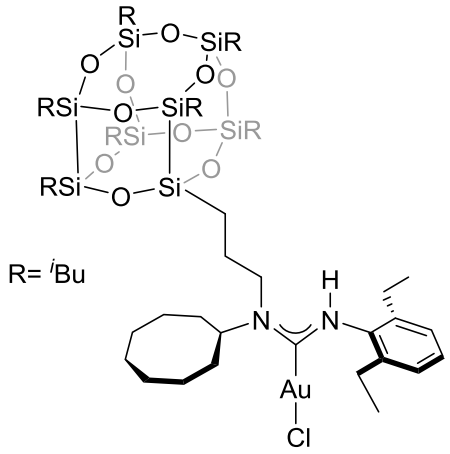


Figure 39. Core structures of acyclic diaminocarbenes (ADC), hydrogen bind supported heterocyclic carbenes (HBHC) and hydrazine amino acyclic carbenes (HAAC).

Early work on the use of ADC-gold complexes in catalysis developed by Hong,[144,224] Hashmi,[225-227] and Echavarren and Espinet[228-231] can be found in two reviews from 2012.[222,223] These studies showed that the activity of Au-ADC complexes is highly dependent on the carbene substitution and, in some of the cases, Au-ADC catalysts lead to different selectivity than gold complexes containing cyclic carbenes (e.g. gold-promoted enyne cyclisation reactions, see Scheme 56).[222,223] It has been proposed that the electronic properties of ADC carbenes direct the ability of Au-ADC complexes to promote alkyne hydration reactions, with the catalytic activity increasing with less donating ligands.[221] Hashmi and co-workers incorporated a silsesquioxane cage to an acyclic aminocarbene (**NHC-158**) and synthesised the corresponding gold complex (Figure 40). [Au(**NHC-158**)Cl] was found to be a very active catalyst, affording remarkably high TON values at very low catalyst loadings in the gold-promoted phenol synthesis and the cyclisation of alkyne-diols to form spiro compounds. [232]



[Au(NHC-158)Cl]

Figure 40. Highly active Au(ADC) catalyst

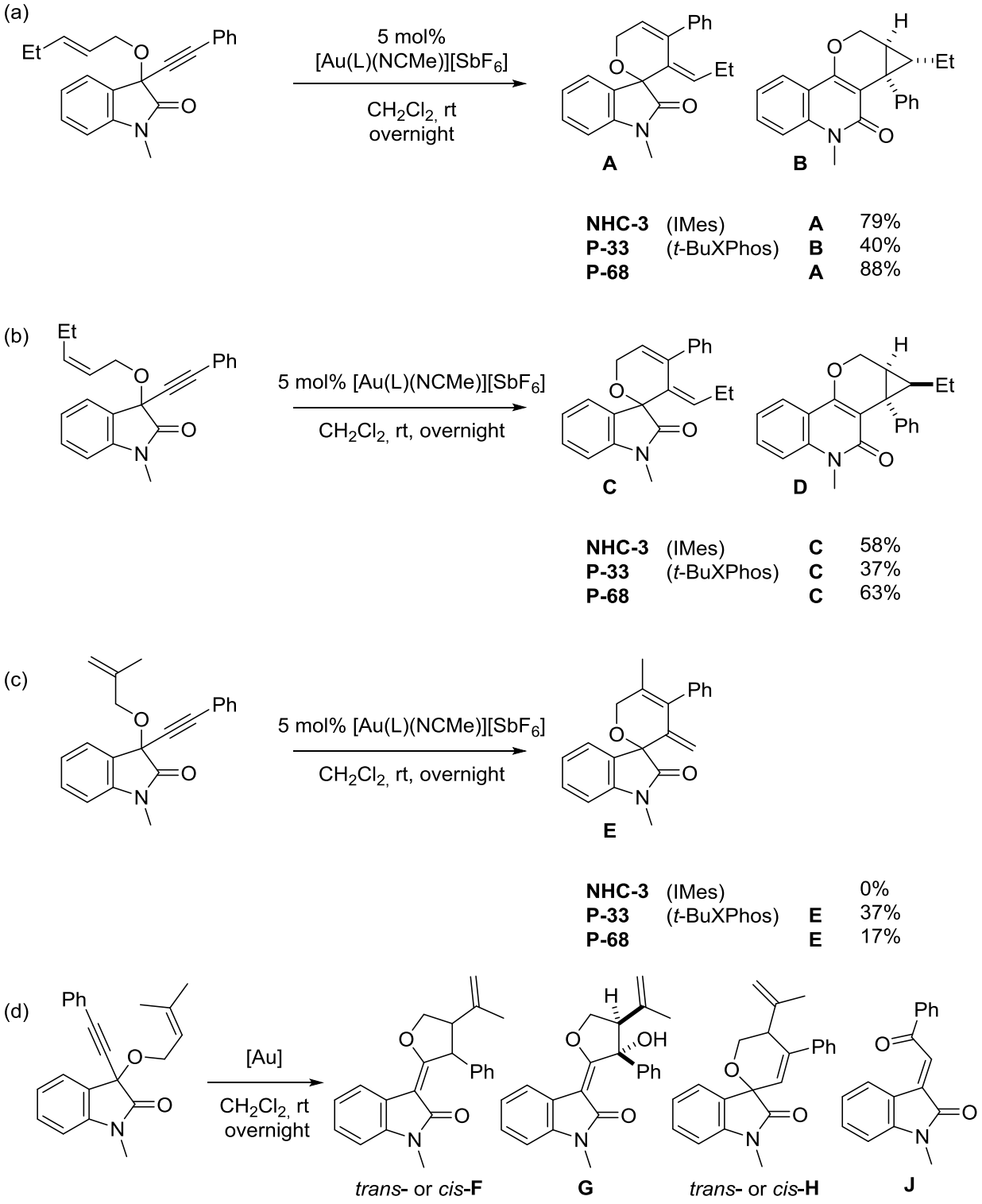
The same group reported the synthesis and catalytic activity of gold complexes containing Hydrazino Amino Acyclic Carbene (HAAC) ligands (Figure 39), prepared via nucleophilic addition of hydrazine derivatives to gold-isocyanide species.[233] These gold complexes were found to be efficient catalysts for the selective synthesis of oxazolines at low catalyst loading.[233] Gimeno, Herrera and co-workers have recently employed Au-ADC complexes to promote the three-component coupling of aldehydes, amines and alkynes in neat conditions to afford propargylamines and indolizines.[234]

4 Wider Comparisons

The majority of this review has separated NHC ligands and phosphorus ligands, and further divided these by structural features, in order to explore the structural diversity of ligands for gold catalysis. However, there are a number of studies that draw comparisons across a wide range of ligands, often spanning these two major classes, and so these are discussed here. Some aspects of this topic have been reviewed elsewhere, although typically with a focus on either phosphorus ligands or NHC ligands.[89,91] The effect of different ligands on fundamental steps of gold-catalysed reactions (electronic activation and protodeauration; both in the presence and absence of significant catalyst decomposition) has been discussed in the first section of this review.[9]

Lee *et al.* carefully examined the effect of ligand structure on the mechanistic pathways in the reaction of oxindole-containing enyne substrates (Scheme 75).[235] [Au(L)(NCMe)][SbF_6] complexes (L = IMes (**NHC-3**), JohnPhos (**P-27**), *t*-BuXPhos (**P-33**), P(O(2,6-*t*-$Bu_2C_6H_3$)$_3$ (**P-68**)) were compared to each other and to [Au(OTf)(PPh_3)]. The structure of the product was a function of the starting material structure and the catalyst, with often quite subtle changes leading to big changes in reaction outcomes (Scheme 75 (a) – (c)). However, catalysts with ligands **P-27** and **P-33** allowed for far more selective reactions than PPh_3-derived catalysts (**P-1**) in some cases (Scheme 75 (d)). This was proposed to be as a result of the catalyst structure influencing the direction of the reaction at various key stages; **P-1**, **NHC-3**, **P-27** and **P-33**, and **P-68** have quite diverse steric and electronic properties. Changes to ligand structure therefore can have an effect not only on reaction rate but lead to new selectivity that can be exploited in organic synthesis.

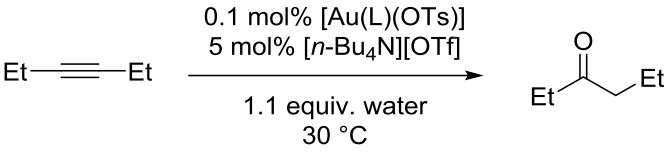
Scheme 75. Studies of reaction selectivity using different ligands. All yields are isolated yields.



[Au(OTf)(PPh_3)]	(10 mol%)	8% *trans*-**F** / 26% *cis*-**F** / 5% **G** / 16% *cis*-**H** / 12% *trans*-**H** / 7% **J**
[Au(**NHC-3**)(NCMe)][SbF_6]	(5 mol%)	0% (starting material recovered)
[Au(**P-27**)(NCMe)][SbF_6]	(5 mol%)	50% *trans*-**F** (91% *trans*-**F** in THF solvent)
[Au(**P-33**)(NCMe)][SbF_6]	(5 mol%)	49% *trans*-**F**
[Au(**P-68**)(NCMe)][SbF_6]	(5 mol%)	17% *trans*-**F** / 30% *cis*-**H** / 13% *trans*-**H**

Gatto *et al.* have conducted a thorough study of alkyne hydration catalysed by LAuX complexes, using diphenylacetylene as a model substrate (Scheme 76).[236] A discussion of counterion effects is beyond the scope of this review, but interesting trends were found for the ancillary ligand also. Complexes with NHC ligands performed the best, followed closely by JohnPhos (**P-27**) complexes. Acyclic diaminocarbenes, tricyclohexylphosphine (**P-12**), an electron-deficient triarylphosphine, and a bulky triarylphosphite (**P-68**) all gave disappointing results for the hydration of 3-hexyne. These results suggest that protodeauration may be rate-determining here. Catalyst decomposition was observed for phosphine-bearing catalysts, but not JohnPhos, suggesting that this bulky ligand may be stabilising the catalyst.

Scheme 76. Studies of reaction selectivity using different ligands. Conversions determined by ^{1}H NMR spectroscopy.



IPr	**NHC-1**	>99%	(3.5 h)
BIAN	**NHC-42**	>99%	(4 h)
SIPr	**NHC-3**	98%	(8 h)
JohnPhos	**P-27**	74%	(5 h)
(2,4-(*t*-Bu)$C_6H_3O)_3P$	**P-68**	17%	(24 h)
PCy_3	**P-12**	6%	(24 h)
PPh_3	**P-1**	3%	(24 h)

5 Summary and Outlook

This review discusses a large number of studies that benchmark ligands for different gold-catalysed reactions. The review focusses on the two main classes of ligands employed in gold(I) catalysis: phosphines and *N*-heterocyclic carbenes. The archetypical examples of these categories are PPh_3, JohnPhos and IPr. These are usually the first ligand choice when researchers are exploring gold-promoted transformations, and have been shown to be excellent ancillary ligands to stabilise $[Au\text{-}L]^+$ fragments. They are commercially available, stable and work well for a wide number of gold-catalysed transformations and have been applied in various target syntheses in the literature. As such, they are often used as representatives of their ligand class. However, ligand properties can have an enormous effect in gold catalysis, not only on the final isolated yield but also on the rate and selectivity of the reaction. In order to optimise protocols, reduce catalyst loadings, and perform challenging transformations, the ligand effect must be considered. This includes not only the characterisation of the electronic and steric properties of the ancillary ligands, but also kinetic studies of the process; without some degree of time-resolved study it is difficult to distinguish between, for example, a catalyst that has a low turnover frequency and one that has a high turnover frequency but rapidly decomposes under the reaction conditions.

Phosphines and NHCs offer multiple opportunities for chemical modification and, in consequence, for the tuning of their electronic and steric properties. In this review, we have surveyed the structural modifications developed in both classes of ligands that have been studied in gold catalysis. These can be approximately divided into three types: those that are designed to deliver enhanced reactivity in a particular reaction type through influencing the steric and electronic properties of the corresponding catalyst; those that are designed to enable specific interactions that may be crucial to the reaction(s) of interest; and those that are designed to function under specific conditions. The latter type includes ligands with solubilising groups to enable water solubility, or ligands that are designed to be switchable in response to a stimulus.

The majority of phosphorus ligands that have been surveyed here are phosphine ligands, although phosphites (for example) have also been deployed. In particular, Buchwald-type (biaryl)phosphine ligands are amongst the most efficacious in a range of reactions. A related series of (aminoaryl)phosphine ligands, which provide a basic/hydrogen-bond accepting moiety, have been shown to be effective (and in many cases essential) for a suite of interesting synthetic organic chemistry reactions. Further modifications of this scaffold to introduce stabilised carbenium or α-cationic functionality can significantly decrease the electron-richness of the ligand (and corresponding catalyst), while substituents such as ylides have significant and opposite effects. The precise requirements for a given ligand will depend on the reaction of interest; reactions with weakly

nucleophilic substrates (e.g. hydroarylation) or that rely on intermolecular nucleophilic attack (e.g. hydroamination) will often benefit from electron-poor ligands, for example.

Many examples of NHC ligands have been reported in the ever-growing field of Au-NHC catalysis. The reports highlighting the ligand effect in these transformations have been organised according to the structural modification which include backbone, wingtip and NHC-core modifications. These reports show the wide number of possibilities of ligand design when it comes to N-heterocyclic carbenes. The steroelectronic characterisation of these ligands has been included whenever available, although the detailed characterisation of the properties of new ligands is not always reported in methodology-driven synthetic chemistry papers.

Across both ligand classes the structural diversity of the ligands that have been deployed in gold catalysis is staggering; these cover sterically small and large ligands, and ligands that range from very electron rich to very electron poor. Different reactions have different rate-determining steps and different possible side-reactions, and this leads to a situation where it is not really possible to state that there is one 'best' ligand for gold catalysis.

It is hoped that this detailed review will allow researchers to identify reactions that best represent those that they wish to perform, and thereby identify the best ligands to test for their particular reaction; in addition, this might give inspiration to researchers who seek to design the next generation of ligands, or who plan to apply new ligands to the ever-growing field of gold catalysis. There remain a number of challenges for the gold catalysis community to address in terms of ligand design:

(1) With the exception of some detailed studies, there remains an insufficient understanding of why some ligands perform better in some reactions, and so considerable further work is needed here. Developments in the analysis of ligand properties and the analysis of how these impact on reaction performance provide new opportunities to fully address this issue: e.g. ligand descriptors and the analysis of these descriptors using techniques such as principle components analysis;[18] linear regression analyses;[237,238]; and machine learning approaches.[239] There is a practical limit to what can be achieved by simply screening ligands for the best yield, and true understanding is best aided by good quality data and robust tools to treat it.

(2) In order to aid researchers in drawing robust comparisons between ligand systems, we would recommend that researchers who are developing new ligands for gold catalysis: (i) use a selection of benchmark reactions under a standard set of conditions; (ii) examine conversion and/or yield at multiple time points; (iii) include one or more readily-available literature systems in the comparison (e.g. with triphenylphosphine and/or JohnPhos and/or IPr); and, ideally (iv) profile the conversion of the reaction over time *versus* a common ligand system. In addition, the role of

silver in gold-catalysed reactions to abstract a halide from a [Au(L)Cl] complex leads to potential complications regarding catalyst speciation;[240] well-defined species that do not require activation by halide abstraction, such as [Au(L)NTf_2], [Au(L)OTf], [Au(L)OH], or [Au(L)(NCMe)]$^+$, may be preferable when drawing comparisons with benchmark ligands.

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7 Author Biographies

Alba Collado studied for her Bachelor's degree in Chemistry at the Universidad Autónoma de Madrid before undertaking her PhD in organometallic chemistry at the University of Zaragoza under the supervision of Professor Miguel Ángel Esteruelas. She then moved to the UK, where she held postdoctoral positions at the University of St Andrews with Professor Steve Nolan and the University of Edinburgh with Professor Guy Lloyd-Jones FRS. She was awarded a prestigious Juan de la Cierva fellowship which she held at the Universidad Complutense de Madrid with Professor Miguel Á. Sierra. Alba then moved to the Universidad Autónoma de Madrid in early 2019 as Profesora Ayudante Doctora where she collaborates with the FRONCAT group. Her research interests span a range of topics in organometallic chemistry and catalysis mediated by organometallic complexes.

David Nelson obtained his MChem from the University of Edinburgh (2008) and his PhD from the University of Strathclyde (2012, with J. M. Percy). He was subsequently a Research Fellow at the University of St Andrews (2012-14, with S. P. Nolan). He established his independent research group at the University of Strathclyde in 2014 as one of the inaugural cohort of Chancellor's Fellows, and was promoted to Senior Lecturer in 2018. He was a Thieme Chemistry Journals Award winner in 2020 and joined the editorial board of *Communications Chemistry* in 2020. His research programme spans organic and organometallic chemistry, with a focus on reaction mechanisms and structure/reactivity relationships.

Steven P. Nolan was born in Canada. He received his BSc in Chemistry from the University of West Florida, and his PhD from the University of Miami (with C. D. Hoff). He was a postdoctoral researcher at Northwestern University (T. J. Marks). He joined the Department of Chemistry at the University of New Orleans in 1990. He moved to the Institute of Chemical Research of Catalonia (ICIQ) as a Group Leader/ICREA Research Professor in 2006, and to the University of St Andrews as a Chair in Inorganic Chemistry and Catalysis in 2009. In 2015 he moved to Ghent University as a Senior Full Professor of Chemistry.

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