Chemical Science
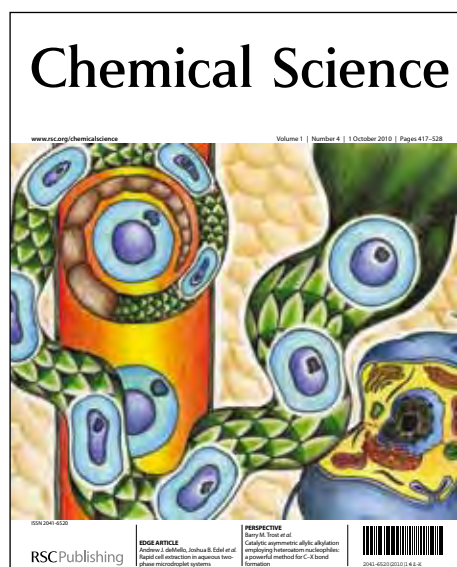
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Chemical Science

Minireview

Hetero-metallic complexes, tandem catalysis and catalytic cooperativity

José A. Mata,[a] F. Ekkerhardt Hahn,[b]* and Eduardo Peris[a]*

This minireview reports the most recent advances in the use of heterometallic catalysts based on single-frame N-heterocyclic carbene ligands. The article describes the synthetic strategies for the preparation of heterometallic catalysts, and their applications in the design of tandem processes, by a combination of the catalytic properties associated to the two or more different metal centers. Several examples in which the use of hetero-metallic complexes results in a clear enhancement of the catalytic outcome, compared to the results provided by mixtures of related homo-metallic complexes are also discussed. The field constitutes a research area that is full of potential and is at its very earliest stage.

Introduction

Due to the restricted number of transition metals available, the advance in the preparation of metal-based catalysts mainly relies on the design of new ligands. Facilitating a complicated catalytic reaction with a simple and effective catalyst, or finding a way for combining several catalytic reactions into a one-pot tandem process,[1] are two of the most important challenges that imply the design of improved catalysts. A straightforward approach for the design of sophisticated tandem processes is to combine two different metal complexes, aiming that each of the metals facilitates mechanistically independent catalytic cycles.[1a, 1c, 2] In such types of processes, each metal center promotes an individual catalytic step, and synergism, or cooperativity is difficult to achieve. It is well accepted that catalysts containing multiple metal centers in close proximity to each other can lead to a better reactivity than the equivalent mixtures of monometallic complexes, in particular for second order kinetic dependence on the catalyst.[2a, 3] In addition, polymetallic catalysts afford a higher nanolocal concentration of the active sites, and this may also lead to better catalytic performances than the analogue monometallic catalysts, as happens in some dendrimers ('dendrimer effect').[4]

The great topological versatility of N-heterocyclic carbenes (NHCs),[5] their wide range of associated electronic properties,[6] and their ability to form stable complexes with a large variety of metal complex fragments,[7] have raised NHCs to a privileged position in the design of all kinds of homogeneous catalysts, including those having more than one metal.[8] Polymetallic N-heterocyclic carbene complexes are normally supported by poly-NHCs, mostly di- or tri-NHCs.[8] Di-NHCs that can be bound to two different metals may allow the preparation of NHC-based dimetallic complexes.[9] The simplest of such type of ligands are those depicted in Scheme 1. Di-NHCs linked by aliphatic chains may lead to either the dimetallic (**A**) or monometallic species with a chelating di-NHC ligand (**B**), mostly depending on the reaction conditions used,[8] while Janus-type bis-NHCs ligands (**C**) are geometrically forced to function as bridges between two metals, therefore favouring the formation of dimetallic complexes. It is also important to take into account that ligands of type **C** tend to establish a fixed metal-to-metal separation while the distance between the metals in complexes of type **A** may vary depending on the relative orientation of the two carbene units due to the flexibility provided by the aliphatic linker.

Over the last few years, we have reported efficient methods for the preparation of homo- and heterodimetallic complexes, mostly based on a 1,2,4-triazolyl-3,5-dyilidene ligand with metals of the platinum group including gold (**D**).[10] The preparation of such heterodimetallic complexes allowed us to study several catalytic processes in which each of the metal centers facilitated mechanistically independent cycles.[11] We also confirmed that the presence of the two different metals furnished catalytic benefits compared to the cases in which mixtures of homodimetallic species were used,[12] in a clear illustration of a synergistic behavior between the metals present
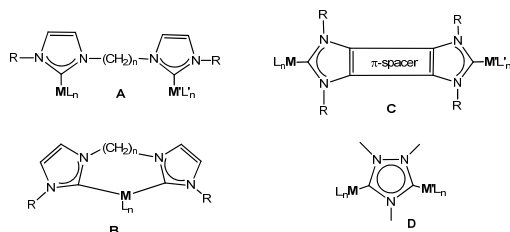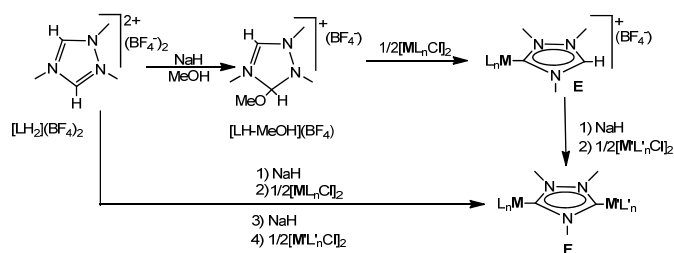

Scheme 1

in the heterometallic unit. Several authors have also reported efficient methods for the preparation of NHC-based heterometallic complexes, such as the representative examples described by Hahn[13] and Cowie.[14] In this article we will emphasize the preparation of NHC-based heterometallic complexes and their use in homogeneous catalysis. We will focus our attention on those examples in which the ligands are purely poly-NHC ligands (mostly di-NHCs), thus not considering all other examples in which the heterometallic complexes are supported by NHC-containing hybrid ligands. The article will describe the preparative procedures leading to the heterometallic complexes, their singular properties in homogeneous catalysed reactions, and the perspectives and potential that this type of novel complexes may bring in the near future.

Preparation of NHC-based heterometallic complexes

Most of the known NHC-based heterometallic complexes are obtained by the sequential coordination of the different metal complex fragments to a single-frame ligand, a process that often implies that the starting poly-azolium salt needs to be sequentially deprotonated. In the case of the 1,2,4-trimethyl-triazolium tetrafluoroborate ($[LH_2](BF_4)_2$), an equimolar amount of NaH affords the methanolic adduct [LH-MeOH](BF_4).[15] This adduct can react with a suitable metal source (normally a dimer of a metal-chloride complex) to afford a triazolium-ylidene-metal complex (**E**), which can be further deprotonated and coordinated to a second metal complex fragment of choice (Scheme 2). The reaction can also be carried out in a one-pot procedure, in which the reaction intermediates ([LH-MeOH](BF_4) and **E**) are used *in situ*, so that the stepwise metallation of the ligand provides directly the heterodimetallic complexes.[10b] The one-pot process is very convenient because it simplifies the reaction workups to give the final products, and is also accompanied by the reduction of the amount of solvents used in the overall synthetic and purification processes.
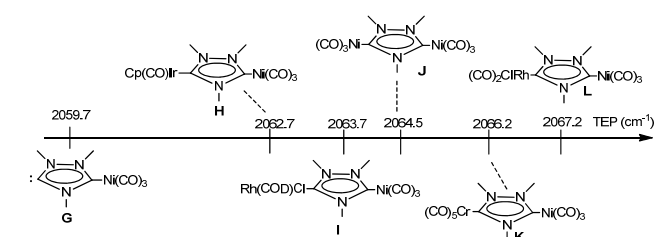

Scheme 2

By adapting this synthetic protocol to the different metal sources, we were able to obtain and fully characterize the hetero-dimetallic complexes **1-9**,[10b, 11a, 11d, 12a, 16] depicted in Scheme 3. Inspection of the X-ray molecular structures of these

complexes indicate that the metal-to-metal distance is in all cases very close to 6 Å.
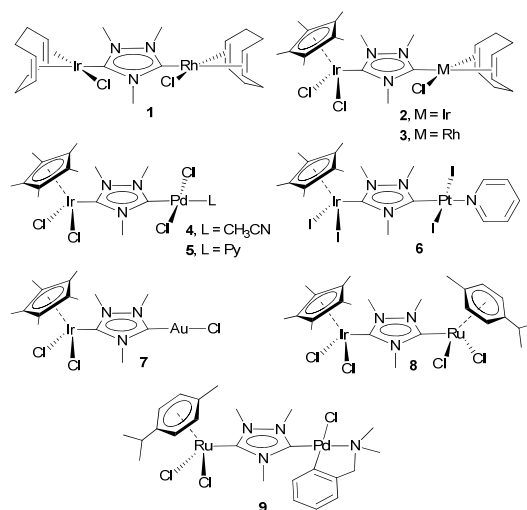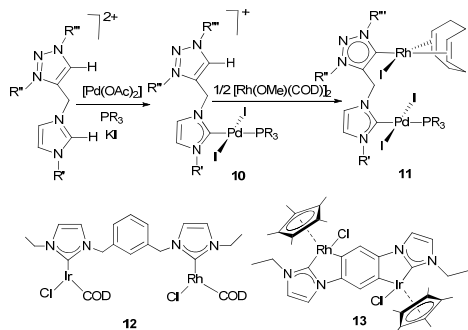

Scheme 3

The analysis of the electronic properties associated with the 1,2,4-triazole-di-ylidene (*ditz*) ligand were performed based on Cyclic Voltammetry (CV) and DFT studies. The CV studies performed for the di-ruthenium and the ruthenium-iridium (**8**) complexes,[12a] revealed that the metal-to-metal electronic coupling is weak, although stronger than the couplings displayed by dimetallic complexes with other Janus-type di-NHC ligands.[17] In particular, the separation between the oxidation bands of a *ditz*-based diruthenium complex was found to be 120 mV, which corresponds to a class II system according to the Robin and Day classification.[18] The σ-donating power of *ditz* was estimated by DFT means, after having proved that the computational methods allow the determination of very accurate values of Tolman-Electronic-Parameters (TEPs) of many other NHC ligands.[19] Interestingly, the TEP value associated with *ditz* may be calculated by considering the ligand in various different coordination modes. If the calculation is performed by considering that the di-carbene ligand is coordinated to one Ni(CO)$_3$ fragment, while having the other end of the ligand uncoordinated (**G**, Scheme 4), then the TEP value is 2059.7 cm^{-1}.[20] Upon coordination of the free-carbene end of the molecule to a second metal complex fragment, an overall change on TEP is observed, the largest being observed for the dinuclear Ni-RhCl(CO)$_2$ complex (**L**), for which Δ(TEP) = 7.5 cm^{-1} compared to **G** was calculate (Scheme 4). This study not only provided with an interesting way to quantifying the metal-to-metal electronic interaction by measuring the variation of the TEP values, but also illustrates how the electron-donating character of Janus di-NHCs may vary depending on the metal complex fragments to which they are bound.
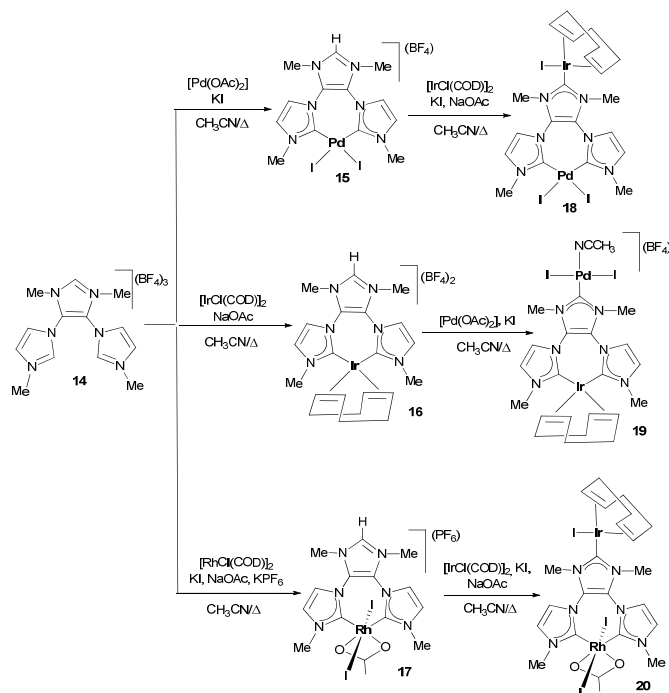
Scheme 4

The sequential deprotonation/coordination of a methylene- or ethylene-bridged di-azolium salts was used by Cowie and co-workers to prepare a series of heterobimetallic complexes with rhodium-palladium,[14a] iridium-palladium[21] and rhodium-iridium[14b] metal centers. In these studies, the authors were able to prepare complexes from the related di-imidazolium, di-triazolium and mixed imidazolium-triazolium salts to afford the desired heterobimetallic complexes. Interestingly, when mixed imidazolium-triazolium salts are used, the first metallation occurs at the imidazolium part, therefore generating a imidazolylidene complex with a pendant triazolium group (10, Scheme 5). This is a consequence of the reduced acidity of the triazolium group compared to the imidazolium group of the pre-ligand, which renders the imidazolium side more easily deprotonated and subsequently metallated.[14a] Unfortunately, as stated above, the use of this type of alkylidene-linked di-azolium salts may also afford the related chelate complexes, therefore sometimes diminishing the selectivity of the process. As a method to prevent the formation of di-NHC chelate complexes, Braunstein and co-workers used a di-imidazolium salt in which the two azolium groups are bridged by a *m*-xylylene unit, which enforces the bridging coordination. By using this salt as a di-NHC precursor, the authors were able to isolate a mono-iridium complex with a pendant imidazolium group, which they used for the preparation of a heterobimetallic Ir/Rh complex (12).[22] The same strategy was later used by Straub and co-workers for the preparation of heterometallic Pd/Au, and Pd/Cu$_2$ complexes, by using an unsymmetrical *m*-xylylene-bridged di-triazolium salt, in which one of the triazolium groups is functionalized with a thiol group.[23] A related methodology employing rigid *p*-phenylene bridge between the imidazolium groups, was recently used by Hahn and co-workers for the preparation of a heterodimetallic Ir/Rh complex (13).[24]
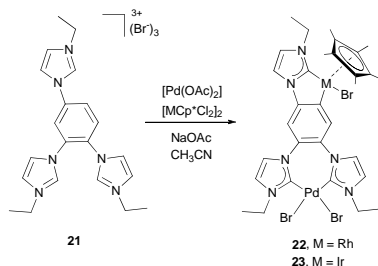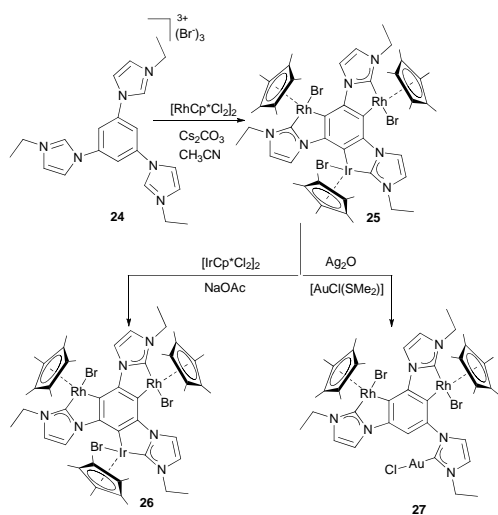

Scheme 5

Scheme 6

Another interesting asymmetric poly-NHC ligand that allows the preparation of heterobimetallic complexes is our recently described Y-shaped tri-NHC, which can be obtained from the tri-imidazolium salt 14 (Scheme 6).[25] This ligand is capable of bridging two metals in two different coordination environments (one chelating, the other monodentate), therefore affording complexes with different reactivities at the two ends of the molecule, regardless whether the complexes are homo- or heterometallic. Interestingly, the stepwise coordination of the ligand is selective, in the sense that the first metal will prefer to bind to the chelating part of the ligand, affording the chelate complex with a remaining imidazolium group. This observation facilitates the preparation of heterometallic complexes, in which each metal can be coordinated to the part of the ligand that we wish, just by adding the metals in the appropriate order, as in the case of the two different iridium-palladium complexes 18 and 19 (Scheme 6). A convenient point in the preparation of the heterometallic complexes,[26] is that the stepwise one-pot synthesis also affords good yields of the final complexes, providing an important simplification of the experimental procedure. Scheme 6 summarizes the general synthetic methodology for the preparation of a series of heterometallic palladium-iridium and rhodium-iridium complexes.[26] The analysis of the X-ray molecular structures of the complexes allowed us to determine that the metal-to-metal through-space distances fall in a narrow range (6.7-7.0 Å), illustrating the rigidity of the ligand.

By using an unsymmetrical tri-imidazolium salt featuring a 1,2,4-substitution of a central phenyl ring (21), Hahn and co-workers were able to metallate simultaneously with two different complex fragments, by taking advantage of the differences in their coordination chemistry.[13b] While the Pd(II)

complex fragment prefers to form a chelate di-NHC complex, the iridium (or rhodium) complex fragment tends to react with the NHC in 4-position with formation of an NHC complex which subsequently orthometalates the phenyl ring (Scheme 7). This is an elegant example of a regioselective metalation of two different metal fragments in a one-pot reaction. The related symmetrical 1,3,5-tri-imidazolium salt (**24**), allows the formation of the corresponding dirhodium complex **25**, by reaction of **24** with [RhCp*Cl$_2$]$_2$ in the presence of Cs$_2$CO$_3$ (Scheme 8). The formation of complex **25**, with a pendant imidazolium group, is very convenient for the preparation of the trimetallic Rh$_2$/Ir complex (**26**) and the Rh$_2$/Au complex (**27**), by reaction of **25** with [AuCl(SMe$_2$)] or [IrCp*Cl$_2$]$_2$, respectively.[13c]
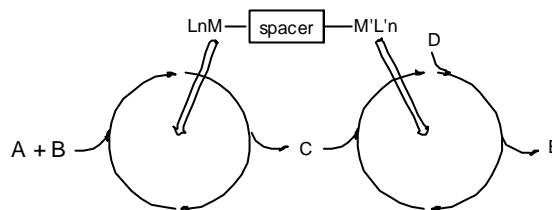

Scheme 7

Scheme 8

NHC-based hetero-metallic complexes in catalysis

The combination of several transition-metal-catalyzed transformations in one single reaction vessel is gaining increasing attention. The strategy often implies the use of two (or more) metal catalysts for two (or more) transformations.[27] A rather logical application of heterometallic complexes is their use as multicatalysts in concatenated multistep processes, which allow the simple preparation of sophisticated molecules in one-pot syntheses. While multicatalysts are starting to flourish in the field of organocatalysis,[28] we are rather surprised that the only examples with metal-based multicatalysts (single

complexes containing two different catalytically active metals) are the ones reported by us, mostly using the triazole-di-ylidene ligand **D** to hold two different metals together. The idea of using two different metals bound by a single-frame ligand to promote a tandem process is extremely simple, and consists in the use of each of the metals to facilitate two (or more) mechanistically distinct (orthogonal) cycles, which may be combined to compose the overall tandem process (Scheme 9). In theory, a heterometallic catalyst may be appropriate for the design of many tandem processes, by a simple combination of all the potential individual catalytic capabilities of each metal site, thus providing a great advantage over traditional monometallic catalysts. Despite the simplicity of this idea, the practical approach to the design of efficient heterometallic complexes of multimetallic catalysis suffers from some important complications, such as: i) the need that the two (or more) catalytic active sites are compatible with the reaction conditions needed for each individual catalytic cycle (and with the residual materials generated in each catalytic step); ii) the possibility that the two metals are being mutually deactivated; iii) the possibility that the single-frame ligand does not provide the stability needed to maintain the heterometallic nature of the catalyst during the whole catalytic process, which may need harsh reaction conditions, or that it may decompose to give mixtures of the related homodimetallic complexes; and iv) the possibility that the two metals display similar reactivity patterns and therefore are able to facilitate any of the cycles comprised in the overall tandem reaction, thus making the use of the heterometallic complex obsolete.
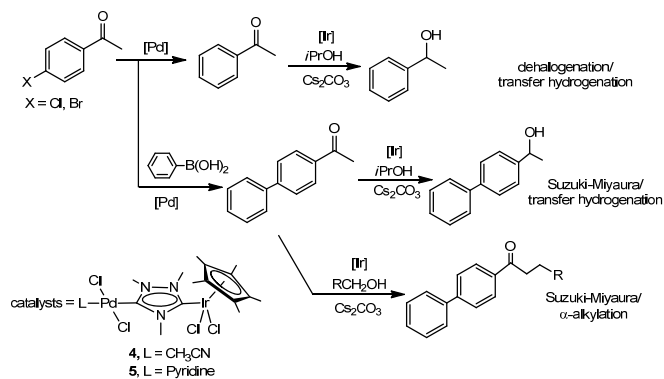

Scheme 9

Probably due to their stability and the high yields observed in their synthesis, most of the NHC-based heterometallic complexes that have been reported to date are Ir/Rh species (see Section 2). In fact, the first *ditz*-based heterometallic complexes that we obtained were **1** and **3** (Scheme 3). In search for a tandem process for which these heterometallic complexes could be used, we ended up by studying the consecutive oxidative cyclization of 2-aminophenyl ethyl alcohol and the alkylation of the resulting indole with a series of primary alcohols (Scheme 10).[10b] In principle, we aimed that the first step of the reaction (cyclization of the amino alcohol) would be catalysed by Rh(I) or Ir(I) complexes, while the second step (alkylation of indole by the primary alcohol) should be catalysed by the Ir(III) part of the catalyst. We found that the most active catalyst for this reaction was the mixed-valence Ir^I/Ir^{III} complex **2** (Scheme 3), but also that other *ditz*-based homodimetallic complexes containing Ir^I/Ir^I and Rh^I/Rh^I were active in the

reaction, although providing lower yields and selectivities. Recently, Grigg and co-workers also demonstrated that [IrCp*Cl$_2$]$_2$ was able to promote both steps of the reaction.[29] Although we believe that our preliminary results were interesting, because we created the basis for the efficient synthesis of heterometallic complexes from the *ditz* ligand, we found it difficult to combine catalytic reactions specifically promoted by Rh^I or Ir^I and Ir^{III}, due to their chemical similarities.
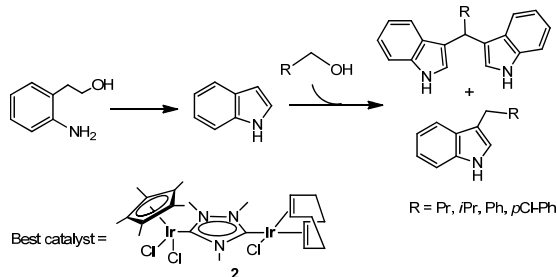
Scheme 10

In order to obtain a dimetallic catalyst able to mediate two fundamentally different reactions, we found the combination of iridium and palladium to be a much better choice, due to the inherent differences in the catalytic behavior of these metals. Both metals are active in a large and distinct library of transformations. We thought that haloacetophenones should be very convenient substrates to start our studies with, because they combine a halide-aryl bond, for which the palladium part of the catalyst should provide a large library of transformations, and a C=O bond, for which iridium may introduce a variety of modifications, most of them based on borrowing-hydrogen processes.[30] We started with the simplest tandem process, implying the dehalogenation/transfer hydrogenation of haloacetophenone (Scheme 11), for which we obtained excellent yields in the production of 1-phenyl-ethanol.[11a] As shown in Scheme 11, by slightly modifying the reaction conditions, we were able to design two more sophisticated tandem processes, namely the Suzuki-Miyaura coupling/transfer hydrogenation (which implied the addition of phenyl boronic acid) to afford biphenylated secondary alcohols, and the Suzuki-Miyaura coupling/α-alkylation of haloacetophenones (by adding a primary alcohol, instead of the secondary alcohol used for the transfer hydrogenation) to yield biphenylated-alkylated ketones.

Scheme 11

All these reactions not only constituted a clear advance over other alternative procedures to the same final products, but also provided a clear illustration of catalytic cooperativity between the two metals comprised in the heterodimetallic unit. As can be seen in Figure 1, mixtures of the homodimetallic complexes of iridium (**28**) and palladium (**29**), afforded significantly lower yields of the final products than the heterometallic complex **5**, for reactions carried out under the same conditions and after exactly identical reaction times. This result constituted first evidence of catalytic cooperativity between the two different metals contained in **4** and **5**.[11a] In a separate set of experiments, the heterometallic Ir/Pd complexes **18** and **19** (Scheme 6) were also tested in the two tandem processes that combined the dehalogenation/transfer hydrogenation, and the Suzuki-Miyaura/transfer hydrogenation.[26] In these two processes both catalysts showed excellent activity, and as demonstrated for **4** and **5**, the activity of the heterodimetallic complexes was higher than the activity shown by the sum of the related monometallic species.[26]
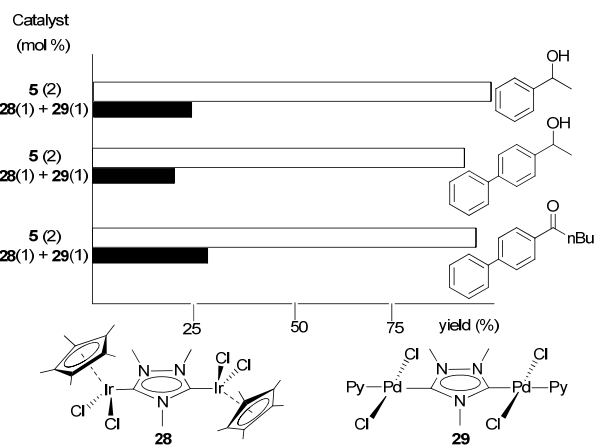

Figure 1. Comparison of the catalytic activity of the hetero-di-metallic complex **5**, with the related mixture of homo-di-metallic complexes of Ir (**28**) and Pd (**29**). The products were obtained according to the reactions depicted in Scheme 10.

The heterometallic Ir/Pd complex **5**, was also used for the synthesis of imines by direct reaction between nitroarenes and primary alcohols.[11c] The reaction implies a two-step tandem process, in which the nitroarene is reduced to an aniline by the primary alcohol, which is subsequently oxidized to the

aldehyde (Scheme 12). The selective coupling of the aldehyde and the amine yield the final imine. In principle, the iridium complex fragment in **5** is thought to facilitate the oxidation of the alcohol to the aldehyde with release of hydrogen. The hydrogen may then be used by the palladium complex fragment for the reduction of the nitroarene to an aromatic amine. The stoichiometric coupling between the amine and the aldehyde affords the final imine. Control experiments were carried out to prove the palladium-containing complexes **5** and **29**, were able to reduce nitroarenes to the corresponding anilines in the presence of H$_2$, while the diiridium complex **28**, was unable to catalyze this reaction under the same reaction conditions, thereby suggesting that the palladium side of the molecule is the one that catalyses the reduction of the nitroarene. On the other hand, the dipalladium complex **29**, was unable to oxidize the primary alcohol to an aldehyde under the reaction conditions used, thus confirming the independent role of the two metals in the overall reaction.
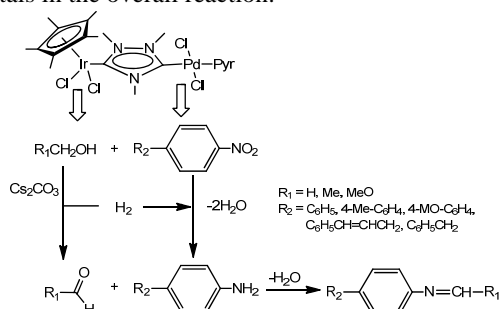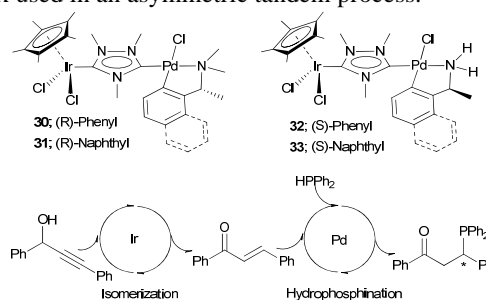

Scheme 12

The same reaction can be combined with the Palladium-catalyzed Suzuki-Miyaura coupling, if halo-nitroarenes are used, as in the reaction between 4-bromonitrobenzene with benzylalcohol in the presence of phenylboronic acid (Scheme 13). This reaction affords the corresponding bisarylated imine in 77% yield, which may be considered as very high, especially if we take into account the sophisticated mechanism for this one-pot synthesis.[11c]
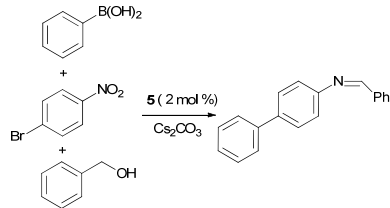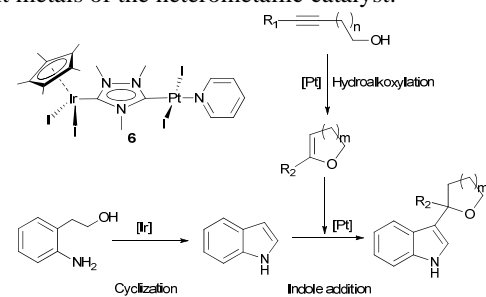

Scheme 13

Aiming to obtain a chiral version of the iridium-palladium catalysts **4** and **5**, we obtained a series of heterometallic Ir/Pd complexes with two axis of chirality related to each metal. The complexes (**30–33**, Scheme 14) were tested in a sequence of two catalytic reactions, namely the isomerization and the asymmetric hydrophosphination of 1,3-diphenylpropargyl alcohol (Scheme 13).[31] Although the catalysts displayed a high activity and regioselectifity, the enantioselectivities were very low (the maximum ee values were 17%). The work constitutes

the first (and so far the only) example, of a heterometallic complex used in an asymmetric tandem process.

Scheme 14

Platinum also constitutes an excellent metal to facilitate many catalytic reactions that in addition can be combined with iridium-catalyzed processes for the design of interesting tandem reactions. With this in mind, we used the Ir/Pt complex **6** for the combination of the iridium-catalyzed oxidative cyclization of amino-alcohols to form indoles,[32] with the platinum-catalyzed multistep reaction of indoles with alkynyl alcohols.[33] The resulting overall tandem process combines three consecutive reactions: i) the oxidative cyclization of an amino alcohol to form indole, ii) the intramolecular hydroalkoxylation of an alkynyl alcohol to afford a cyclic enol ether, and iii) the addition of indole to the unsaturated bond of the enol ether (Scheme 15).[16a] Interestingly, as previously observed for the Ir/Pd complexes **4** and **5**,[11a] the use of **6** provides an improved catalytic outcome compared to the mixture of the related homodimetallic analogue complexes (Figure 2), thus suggesting that catalytic cooperativity should be at work between the two different metals of the heterometallic catalyst.
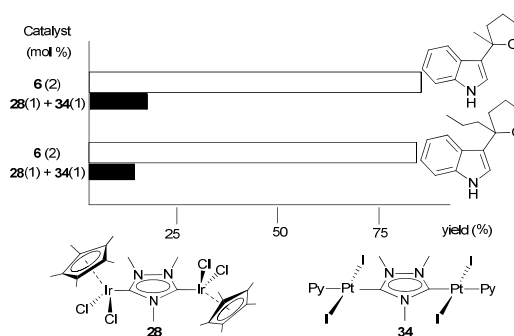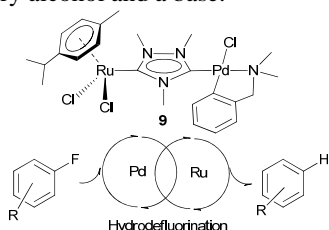

Scheme 15

Figure 2. Multistep functionalization of indole by the multistep reaction between an alkynyl alcohol and an amino alcohol. The graphic compares the activity of the

Ir/Pt hetero-metallic complex **6** with the activity of the related homo-dimetallic complexes **28** and **34** (reactions carried out under the same reaction conditions).

The combination of Ru and Pd in complex **9**, also gives access to a very promising library of catalytic reactions that may be combined into sophisticated tandem processes. Together with the myriad of catalytic applications of the palladium complex fragment, we may think of adding the rich chemistry of ruthenium in C-C bond formation reactions through C-H activation.[33-34] However, we decided to test the catalytic activity of this complex in a much simpler but equally challenging reaction: the hydrodefluorination of organic molecules (Scheme 16).[35] This reaction occurs in two steps: first, the C−F bond has to be broken, and then a hydrogen atom has to be introduced by using a convenient hydrogen source (typically high-pressure H_2, silanes, etc.). In general, the ease of the hydrodehalogenation follows the order I > Br > Cl >> F, which is related to the order of C−X bond strengths (C−F bonds are typically 110 kcal/mol, thus being the strongest σ-bond to carbon). We thought that the Pd/Ru complex **9** had the potential to be a good catalyst for hydrodefluorination, because the palladium complex fragment should be able to break the C−F bond, while the ruthenium part of the catalyst should facilitate the reductive step of the reaction, by providing hydrogen *via* an alternative hydrogen source, namely the transfer hydrogenation using a secondary alcohol and a base.

Scheme 16

Complex **9** proved to be a very efficient catalyst for the hydrodefluorination of a wide variety of fluoroarenes, affording quantitative yields in very short reaction times, and very mild reaction conditions (*i*PrOH, 80ºC).[16c] More interesting is the fact the combination of the two different metals is necessary to promote the process, as clearly shown in Figure 3, where the independent use of the homodimetallic complexes of palladium (**35**) and ruthenium (**36**) affords negligible yields of the desired reaction product. Although a mixture of the two different homodimetallic complexes of palladium and ruthenium (**35** + **36**) seem to partially facilitate the process, the reaction clearly benefits when the two different metal fragments are linked by the single-frame ligand, in line with the above mentioned results that support the idea of the catalytic cooperativity between the two vicinal metals in **9**.[16c]
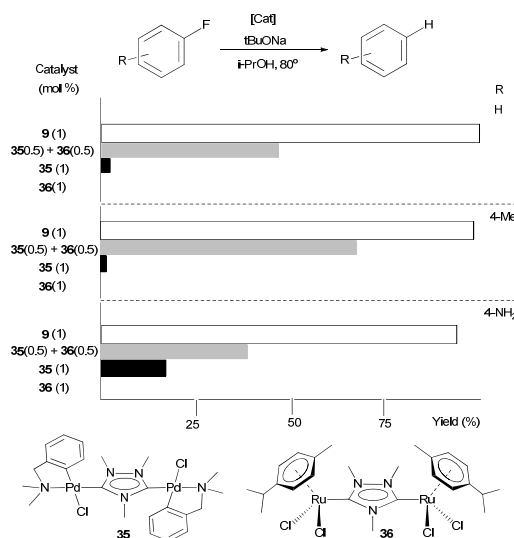
Figure 3. Hydrodeflurination of aromatic substrates. The graphic represents a comparative study on the activity of the hetero-di-metallic complex **9** with the homo-dimetallic analogues, **35** and **36**. All reactions carried out under the same reaction conditions. Yields after 1h.

Encouraged by these results, we decided to test the catalytic activity of **9** in the hydrodefluorination of the more inert aliphatic C−F bonds, for which the reaction with a series of trifluoromethyl-toluenes was tested. Some of the obtained results are listed in Scheme 14.[16c] All these results suggested that catalyst **9** behaves as an effective two-component catalyst, which provides clear benefits in the hydrodefluorination of a wide set of organic substrates.
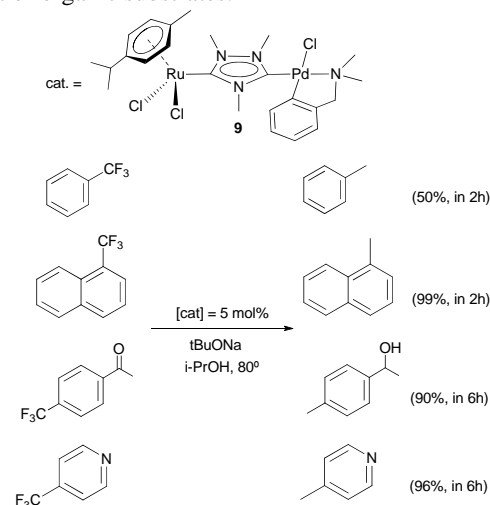
Scheme 17

Conclusions and future perspectives

In the search of more efficient ways for preparing complex organic architectures, there has been an increasing effort in finding multitopic/polymetallic catalysts that may be active for a wide set of organic transformations. The combination of fundamental catalytic steps implying simple and accessible substrates can then lead to sophisticated molecules. The work that we have presented here represents a clear example of a

very logical approach to the design of effective multimetallic catalysts for tandem processes. From the very simple idea of supporting two orthogonal metal fragments with a single-frame ligand, we have obtained a series of heterodimetallic catalysts that are suitable for the design of multiple tandem processes by combination of the catalytic activities associated to each metal fragment. In most of the cases, the combination of the two metals into a single compound, provides with an extra benefit, as shown by the better catalytic outcome of the bimetallic catalyst, when compared to the activity provided by the mixture of the related homo-metallic analogue complexes. Because we do not have a clear explanation for this catalytic cooperativitity, we believe that further study on this effect is needed, in order to establish the clear basis of the design of future heterometallic catalysts.

As stated in the first few lines of the report published on the occasion of the workshop: 'Opportunities for Catalysis in the 21st Century', '*The road to increased activity and selectivity is paved by a myriad of structures that will teach us by experience their connections to activity and selectivity. Thus, we need to create new types of catalyst structures and new methods for catalyst preparation to provide the data and experience to show what makes a catalyst active and selective. To date, synthesis of catalysts has often consumed more time and more effort than the testing of these catalysts. Thus, we must open the bottleneck of catalyst synthesis by learning better methods to prepare families of catalysts.*'[36] We hope that the work described in this article will serve to open the bottleneck in catalyst synthesis, by inspiring future researchers in the design of efficient multimetallic catalysts that may be used for the simple access to sophisticated organic molecules.

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^a Dpto. de Química Inorgánica y Orgánica, Universitat Jaume I, Avda. Sos Baynat. E-12071-Castellón. Spain. Fax: (+) 34 964387322; Tel: (+) 34 964387518; E-mail: eperis@qio.uji.es
^b Institut für Anorganische und Analytische Chemie, Westfälishce Wilhelms-Universität Münster, Corrensstraße 30, D-48149 Münster, Germany, Fax: (+) 49 2518333108; Tel: (+) 49 2518333111; E-mail: fehahn@uni-muenster.de

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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Minireview

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Hetero-metallic complexes, tandem catalysis and catalytic cooperativity

José A. Mata,[a] F. Ekkerhardt Hahn,[b]* and Eduardo Peris[a]*
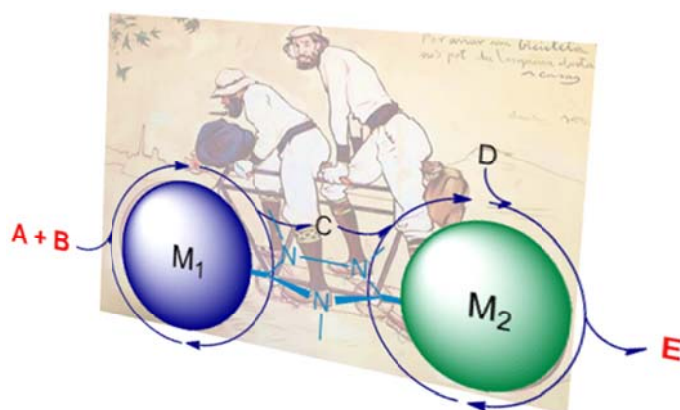
N-Heterocyclic carbene-based heterometallic complexes have emerged as useful multicatalysts for tandem reactions