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PROJECT FINAL REPORT

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4.1 Final publishable summary report

SUMMARY

The **hydroacylation reaction (HA)** is a potentially powerful transformation in organic synthesis. The transformation of an aldehyde and an unsaturated hydrocarbon into a ketone involves C-H activation with C-C bond formation under atom-economical conditions. The main limitation of this reaction is the possible decarbonylation of one of the reaction intermediates. The most common catalysts for these processes are rhodium diphosphine complexes. The research proposal aimed the control of the undesirable decarbonylation pathway achiving by both attenuating decarbonylation and promoting the (rate limiting) reductive elimination step of the final product. The previous works in the host group demonstrated that hemilable ligands attenuate the decarbonylation and also complexes bearing small bite angle accelerated the main reaction.

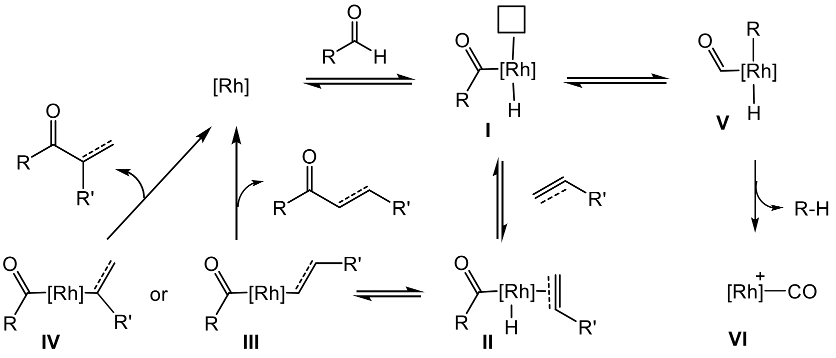
Combining these two antecedents, we have synthesized a new family of rhodium complexes containing hemilabile small bite-angle diphosphine ligands (4th generation Weller-Willis catalyst). The new rhodium complexes were excellent catalyst for the intermolecular hydroacylation of a wide variety of inactivated alkene with β-substituted aldehydes. They were remarkably resistant to decarbonylation, allowing substrate recharged without loss in conversion. A detailed mechanistic study (rate, order and labelling studies) allowed us to understand the reaction mechanism and the reasons behind the high activity and selectivity of these catalysts.

The most used diphosphine ligands were changed by the novel NHCP ligand, both can show small bite angle when they are coordinated to the metal centre. The novel complexes showed to be active and selective for the intermolecular hydroacylation of alkynes with β-substituted aldehydes. Until the date and according to our knowledge there is any study of metal-mediated catalysed reactions employing this class of NHCP complexes.

SUMMARY PROJECT AND OBJECTIVES

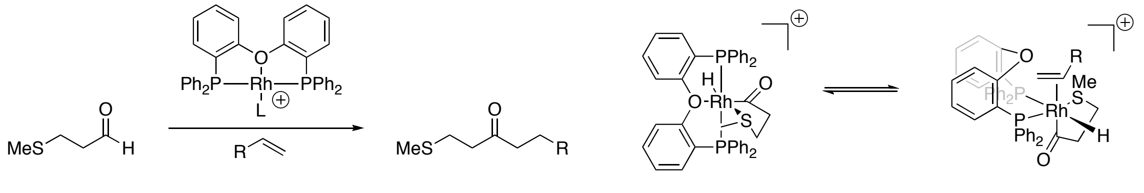
The metal-catalysed hydroacylation reaction is a member of a select group of reactions that combine C-H activation with C-C bond formation in a manner that delivers true atom-efficiency.[1] Given the ready availability of aldehydes and alkenes in both chemical feedstock streams and in fine chemical synthesis, hydroacylation has the potential to be very general and immensely powerful reaction.

Bosnich and Fairlie demonstrated that cationic rhodium(I) complexes, based upon $[Rh(dppe)]^+$, could perform the cyclization of 4-pentenals with excellent turnover rates and numbers, and their detailed mechanistic examination of the catalytic cycle provided the basis of the catalyst–system now utilized for most intramolecular hydroacylation reactions.[2] The most accepted mechanism for this kind of systems involves aldehyde oxidative addition to give an acyl hydride intermediate **I** followed by alkene or alkyne coordination and linear or branched hydride insertion to give intermediates **III** or **IV** respectively. Finally, reductive elimination of the product completes the cycle and is generally accepted to be turnover limiting for alkene hydroacylation.[3] The main limitation is a deleterious side-reaction; reductive decarbonylation is competitive with alkene or alkyne coordination. It is an irreversible process that forms an inactive metal-carbonyl **VI** (Scheme 1).[4]



Scheme 1 Mechanism for Hydroacylation reaction

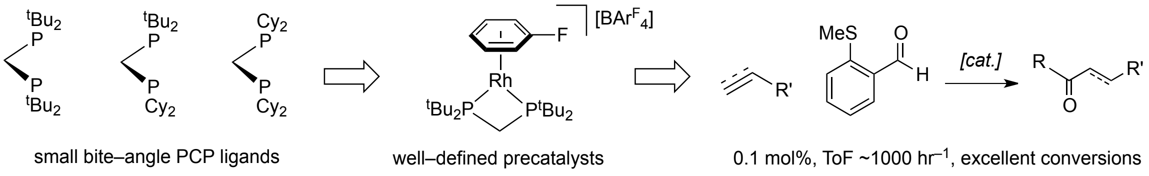
The use of β-S-substituted aldehydes can avoid the reductive decarbonylation. The β-thio group has several roles, including facilitating oxidative addition and filling a vacant coordination site.[5] In the last years the host group has been working in the development of new cationic fluorobenzene rhodium complexes for use in this kind of reaction. Systems containing DPEPhos ligand (2nd generation) have demonstrated that the decarbonylation process can be slowed; the ligand can stabilized the metal centre via hemi-lability, but also give a slow catalyst (Scheme 2).[6]



4 5 6 7

Scheme 2 Second Generation hemilabile ligands for Intermolecular HA

Complexes containing small bite-angle diphospine ligands (3rd generation) have showed high activity for the HA reaction and the reductive elimination of the ketone is accelerated. Using this 3rd generation of catalyst a large amount of terminal alkenes and alkyne were used but only one internal alkene.[7] These well-defined systems are excellent catalysts for hydroacylation using β-S-substituted aldehydes for a wide variety of alkenes and alkynes (Scheme 3), operate at only 0.1 mol% catalyst loading and with turnover frequencies of >1000 hr^{-1}, and represent a breakthrough in catalyst efficiency and rate for the hydroacylation reaction, which is typically run at 5-10 mol%.



small bite–angle PCP ligands

well–defined precatalysts

0.1 mol%, ToF ~1000 hr^{-1}, excellent conversions

Scheme 3 Cationic Rhodium complexes with Hofmann PCP ligands that are outstanding catalysts for intermolecular hydroacylation

With this background in account a new project with the next objectives was designed:

<u>Synthesis of New Ligand Systems</u>: Given the role that a hemilabile ligand or additional solvent molecule has been shown to play in attenuating decarbonylation in DPEPhos and PCP systems, respectively, a clear target is the synthesis of **small–bite angle ligands** with **hemilabile** groups.

The same procedure used in the host group for coordination of the ligands to Rhodium is used for the new systems.

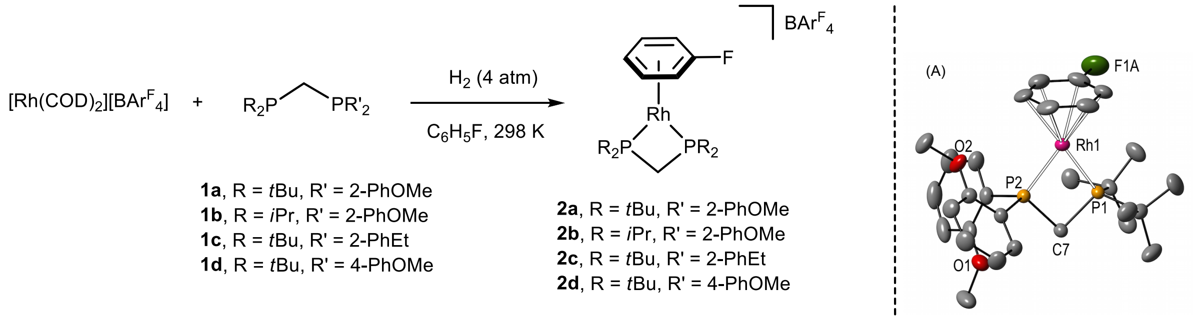
Catalysis testing (recharge): with the new compounds in hand they are tested in the reaction of hydroacylation of 1-octene and 1-octyne with β-S-aldehydes. In collaboration with Willis group (from Oxford) the best catalysts are tested in a large number of reactions employing, external, internals, activated and non-activated alkenes and alkynes.

Mechanism studies: in order to benchmark the mechanistic studies it is vital that good experimental and kinetic data be obtained for each key step. In addition, NMR data can often be obtained for these intermediates. Depending on the system, different processes can be probed: oxidative addition, coordination, insertion, reductive elimination and decarbonylation. Where individual rates cannot be determined, the effects of isotopic substitution (D for H) can be measured as a kinetic isotope effect (KIE).

MAIN S&T RESULTS/FOREGROUNDS

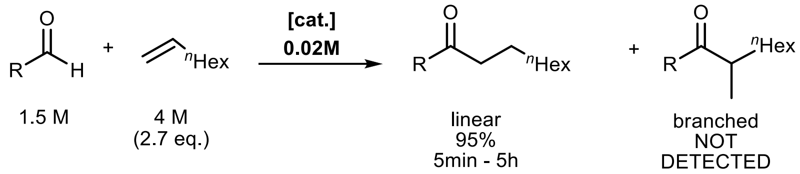
- **PCP hemilable and non-hemilable ligands**

Synthesis of complexes: The ligands **1a** to **1d** were prepared according with the procedure described by Hoffmann and co-workers[8] with some modifications. The reaction of these ligands with $[Rh(COD)_2][BAr^F_4]$ in C_6H_5F and subsequent hydrogenation yield **2a** – **2d** after the precipitation with pentane (Scheme 4). These ligands provide to their corresponding metal complexes different topological and electronic properties. **2a** contains tert-butyl and 2-phenylmethoxy substituents, **2b** iso-propyl substituents instead tert-butyl, **2c** is sterically similar to **2a** but electronically different containing phenylethyl substituents and **2d** with methoxy group in para position. The new complexes were fully characterized by NMR spectroscopy, ESI-MS and elemental analysis. The solid states of **2a** (in scheme 3) and **2b** have also been determined by crystal X-ray diffraction.



Scheme 4 Synthesis of Rhodium diphosphine complexes

Catalysis: In order to compare the effect of the different diphosphine ligands in the catalytic activity of their corresponding complexes, the new Rh-complexes were screened in the hydroacylation reaction. First we compared the activity of **2a** in the hydroacylation reaction of 1-octene and 1-octyne with 2-(methylthio)benzaldehyde. With the preference for alkene over alkyne hydroacylation, full conversion to the product in 5 min and 1 h respectively, we decided to carry out a screening of the activity of the rest of catalysts in the reaction of hydroacylation using 1-octene (Scheme 5). The reactions were carried out under a large excess of alkene (4 M) in order to avoid reductive decarbonylation and the subsequent formation of an inactive metal-carbonyl. The process is very selective in the production of linear ketone; in any case branched ketone was detected.



Scheme 5. Hydroacylation reaction of 1-octene with 2-(methylthio)benzaldehyde

The results demonstrate that **2a** was the most efficient catalyst achieving full conversion in 5 minutes. Remarkable that the rest of the catalyst were also very active (full conversion after 1h-5h), there is no decarbonylation which stop the reaction. When 0.1 mol % of **2a** was used, the catalyst was still active after 15 hours. It seems that **2a** is very stable in front of the decarbonylation

Kinetics and recharged: Comparing **2a–d** and previously reported **[(dtbpm)Rh(FB)][Bar^F$_4$] (2e)**, using 1–octene/β-S-aldehyde , all followed a first order profile for the production of ketone under these conditions; **2a**, **2c** and **2e** could be recharged with twice under a large excess of alkene (2.7 equivalents). **2d** was inactive on recharging. Slower catalysis on each recharge is accounted for by product inhibition, as shown by use of a product:aldehyde:alkene mix of 1:1:2.7 that proceeds at a rate similar to that measured for the reuse of **2a.** Reducing the aldehyde:alkene ratio to a more equitable 1:1.5 ratio shows that catalyst **2a** can still be reused to effect 100% conversion, whereas **2c** or **2e** were essentially inactive. Below ratios of 1:1.3, catalysis did not reach completion suggesting catalyst decomposition. Variation of catalyst **2a** loading between 0.01M and 0.04M, showed a first order dependence, in contrast to reports where bimetallic cooperativity is proposed.[9] Overall, these data demonstrate the positive effect that *o*–C_6H_4OMe has on the ability for the catalyst to operate, and be reused, at low relative alkene loadings or with an internal alkene, when compared to ^{t}Bu (i.e. **2e**).

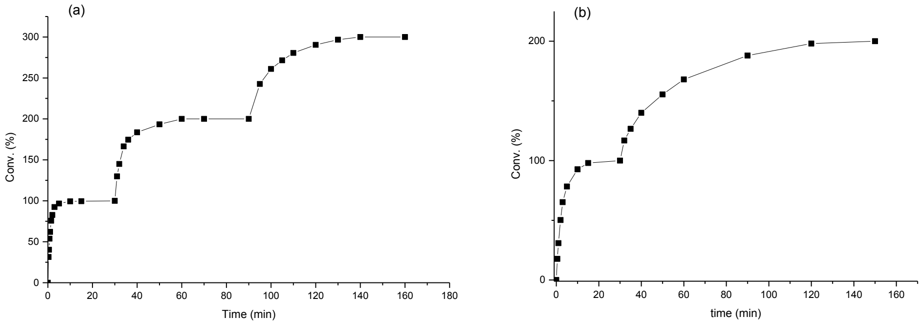
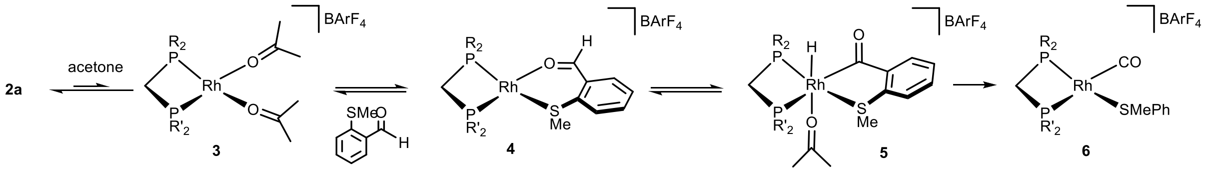


Figure 1. Recycled of 1a. (a) 1.5 M aldehyde, 4 M alkene, 0.02 M of catalyst. (b) 2 M aldehyde, 3 M alkene, 0.02 M of catalyst

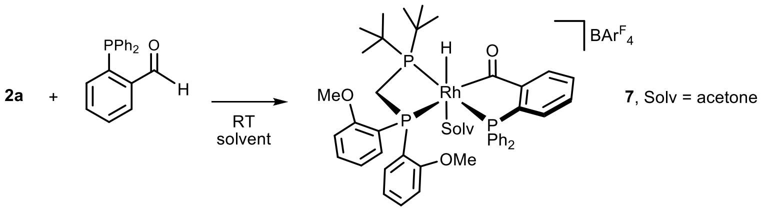
Labelling studies: One of the most common techniques for studying reaction mechanisms is the measurement of the kinetic isotope effect (KIE). This parameter is the ratio between reaction rates shown by two different isotopically labeled molecules in a chemical reaction. When the deuterated and non-deuterated aldehyde is used the small KIE ~ 1.4 is similar to other systems in which reductive elimination is proposed to be turnover limiting step.[10] The reaction was carried out under standard conditions using deuterated aldehyde, deuterium content was found with a 40:60 distribution between α and β positions in the product. When the reaction was followed by ^{1}H NMR a small signal corresponding to the proton of the non deuterated aldehyde was detected (10.16 ppm) until the end of the reaction. When 2-[D]-1-octene was used the same isotopic distribution was observed. This fact implies a fast and reversible hydride insertion giving linear and branched intermediates.

Stoichiometric studies: When the complex **2a** is dissolved in acetone the acetones adduct was observed (**3**). Adding 1 equivalent of 2-(methylthio)benzaldehyde to this mixture a new equilibrium containing several intermediates is resulted. The concentration of the new species is changing quickly but some of them could be detected by ^{1}H NMR (**4** and **5**). After 2.5 hours there is full conversion to the decarbonylation product **6**.



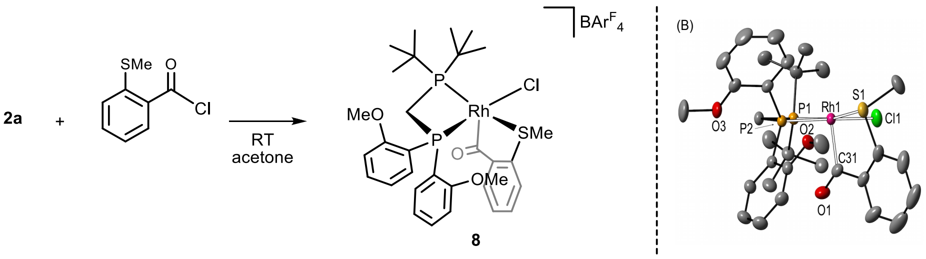
Scheme 6

In order to avoid the decarbonylation and to study the model complex the same reaction was carried out using 1 equivalent of 2-(diphenylphosphino)benzaldehyde (Scheme 7). The strongly coordinating nature of the phosphine allows the formation of the acyl hydride complex **7**. Unfortunately crystals suitable for a X-ray were not obtained however NMR data indicate that the phosphine and acyl group lie coplanar and the hydride ligand in an axial position and trans to the solvent ligand. There was any evidence about methoxy interaction.



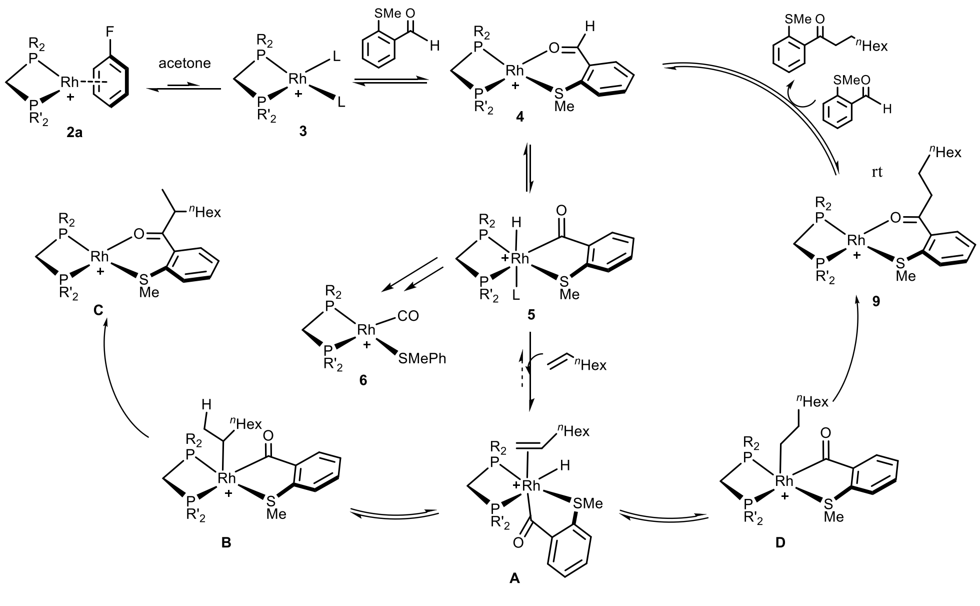
Scheme 7. Formation of Acyl Hydride Complex 7

A clean oxidative addition proceeded when 1 equivalent of acyl chloride is added to **2a** (Scheme 8). The orientation of the new product **8** is different, a five-coordinate Rh^{III} complex with an acyl group trans to a vacant site and the chloride trans to a phosphine as the solid-state structure determined by single crystal X-ray diffraction demonstrates. Also NMR dates are consistent with this description.



Scheme 8. Formation of Acyl Chloride Complex 8

Proposed mechanism: With all the results in mind we can propose the reaction mechanism (Scheme 9). First the fluorobenzene ligand is replaced by acetone, the presence of the aldehyde forms the corresponding adduct (**4**) followed by the oxidative addition to form the hydride intermediate **5**. At this point under no presence of alkene reductive decarbonylation occurs, in less than 3h there is full conversion to the inactive product **6**. The presence of alkene stops the reductive decarbonylation, the coordination of the alkene to form **A** it must to be quasi irreversible.



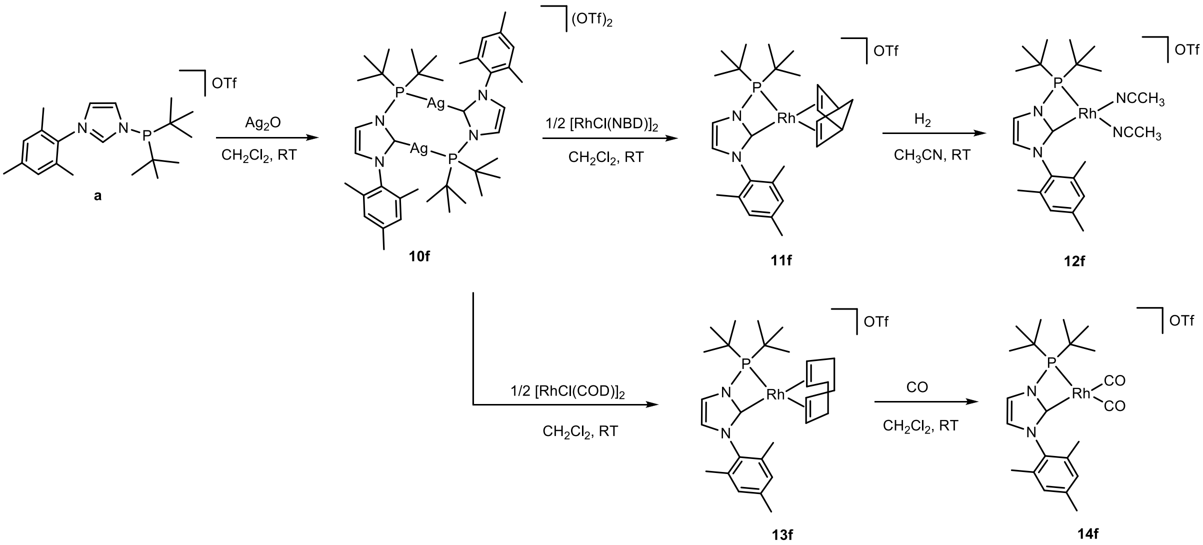
Scheme 9. Proposed mechanism for hydroacylation reaction using 2a.

Coordination is followed by hydride insertion which can result in branched (**B**) or linear intermediate (**D**). Formation of the branched intermediate is reversible explaining why the deuterium is detected in alpha and beta positions when the deuterated aldehyde is used. The reductive elimination is very slow and it does not occur because no branched product is detected, the beta elimination must to be very fast. In the case of the linear hydride insertion must to be also reversible, this can be supported by the presence of the deuterium in both positions when the deuterated alkene is employed. The reductive elimination must to be the turnover limiting step. Finally the release of the ketone from the product adduct complete the cycle.

In collaboration with Prof. Michael Willis from the University of Oxford we explored the scope of the new catalyst **2a** in intermolecular alkene hydroacylation reactions. High yields were achieved with substrates that have previously proved difficult, or completely inactive in this reaction.

- **PNC hemilable and non-hemilable ligands**

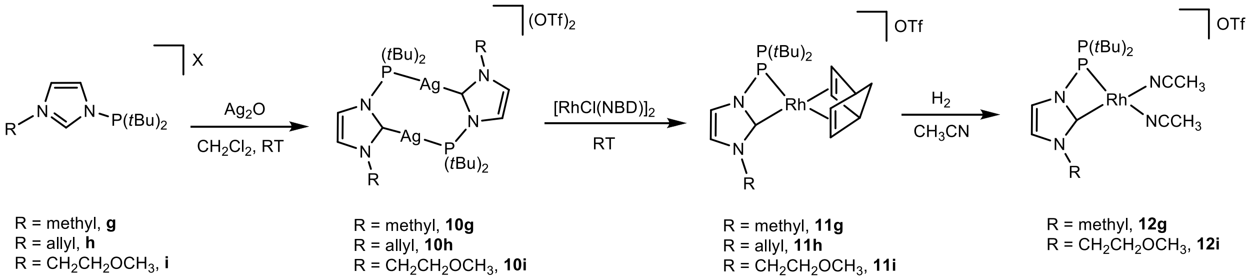
The reaction of the previously reported phosphine-imidazolium salt **f**[11] with Ag_2O in dichloromethane at room temperature gave the dinuclear carbene complex **10f** (Scheme 10).



Scheme 10 Synthesis of Cationic (^{Mes}CNP, k-C,k-P) Silver Dimer Complex and (^{Mes}CNP, k-C,k-P) Rhodium Complexes.

It structure was determined by X-ray diffraction, very similar to that Ag(I) complex containing imidazolin-2-ylidene ligand reported in the literature.[12] The molecular structure shows each silver centre with identical coordination sphere containing one NHC and one P in a quasi linear trans position where the $C_{carbene}$-M-P bond angle is 169.95(6)°. The internuclear Ag-Ag distance, 2.812(4), is slightly longer than its analogue dimer containing a saturated ligand (2.768(1)). **10f** was transmetallated to $[RhCl(diolefine)]_2$ to form **11f** (diolefine = NBD) and **13f** (diolefine = COD) (Scheme 10). The transmetallation was confirmed by NMR, the ^{31}P NMR spectra of Rh(I) complexes show a doublet at 121.6 ppm for **11f** and at 111.8 ppm for **13f** with similar coupling constant of $^2J_{PRh}$ = 140 Hz and 133 Hz respectively. The solid state of **13f** has been determined by crystal X-ray diffraction, as Pt or Pd[11] complexes previously reported containing the same ligand, the geometry around the metal center is distorted square planar with a significant small bite angle of 67.9(3)°.The hydrogenation of COD ligand did not work when **13f** was stirred in acetonitrile under H_2 pressure, any change was detected by NMR. However, when **11f** was used the NBD was hydrogenated to give the complex **12f**. The chemical shift in the ^{31}P NMR changed showing a doublet at 131.6 ppm with of coupling constant of $^2J_{PRh}$ = 184 Hz slightly higher than the olefin analogue complexes. Two different chemical shift were observed in the ^1H NMR for the protons of the acetonitrile ligands a singlet at 2.21 ppm and a broad signal at 1.67 ppm, there is a remarkably difference between the trans influence of the NHC unit and the P-moiety.

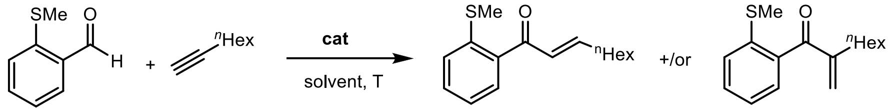
The same procedure was used to synthesized a new two Rh(I) complexes (**Error! Reference source not found.**). Three phosphine-imidazolium salts were employed where only the N-substituent was changed. The previously reported salt **g** contains a methyl group, **h** with an allylic group and, finally**, i** bearing a hemilable substituent. The NBD-complexes were obtained in good yields (70-88%) from the corresponding bimetallic Silver complexes. Complexes **11g** and **11i** were hydrogenated in acetonitrile to obtain **12g** and **12i** respectively. The NMR spectra of **12i** did not show any evidence about the hemilabilty of the O atom to the metal centre, the signal corresponding to the protons of the methoxy groups appeared as a singlet at 3.31 ppm, similar chemical shift for **11i** (3.24 ppm) and for the imidazolium salt **i** (3.38 ppm).



Scheme 11. Synthesis of Cationic (^{R}CNP, k-C,k-P) Rhodium Complexes.

Until the date and according to our knowledge there is any study of metal-mediated catalyzed reactions employing this class of NHCP complexes. Due to the similar structural motifs of the novel ligand and the typical bisphosphino ligand an screening of the new acetonitrile adduct complexes were carried out in the hydroacylation reaction between 2-(methyl)benzaldehyde and 1-octyne to give the linear or/and branched ketones. An equimolar amount mixture of substrates were used, it is demonstrated that the decarbonylation using acetonitrile complexes is slower than when flurobenzene or acetone adducts are used allowing decrees the quantity of 1-octyne used working in economic atom conditions. Focused on Rh-NHCP complexes **12f** is the most effective even at room temperature. The conversion was improved when the counteranion is changed to $BAr^F{}_4$ by reaction of **12f** with $NaBAr^F{}_4$. The replacement of the mesityl group with a potentially hemilable ligand (**12i**) did not imply any improvement. And when **12g** is used a poor conversion is showed. The catalytic activity was compared with the activity of $[(\textit{t}Bu)_2PCH_2P(\textit{t}Bu)_2Rh(NCCH_3)_2][Bar^F{}_4]$ (**13**), previously reported, and which fluorobenzene analogue shown an excellent activity in the hydroacylation of alkenes. Also the activity of $[(\textit{i}Pr)_2PNCH_3P(\textit{i}Pr)_2Rh(NCCH_3)_2][Bar^F{}_4]$ (**14**) was tested, which fluorobenzene analogue demonstrated high selectivity in hydroacylation of alkynes.

Table 1. Screening of Rh-catalysts in HA reaction between 2-(methyl)benzaldehyde and 1-octyne.



Catalyst	Cat. Load.	Solvent	Temp. (°C)	Time (h)	Conv. (%)	Ratio l:b
12f	1	acetone	25	18	76	95:5
12f	1	dcm	25	18	95	99:1
12f	5	dce	50	3	90	97:3
12f	1	dce	50	3	72	97:3
12f-	5	dce	50	3	95	97:3
12g	5	dce	50	3	40	95:5
12i	5	dce	50	3	62	96:4
13	5	dce	50	3	99	69:31
14	5	dce	50	3	96	94:6

In collaboration with Prof. Michael Willis the number of alkynes has being extended in order to show the selectivity of **12f**.

[1] A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182-1195; B. Bosnich, *Acc. Chem. Res.* **1998**, *31*, 667-674; cM. C. Willis, *Chem. Rev.* **2010**, *110*, 725-748.

[2] D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 946-954.

[3] M. von Delius, C. M. Le, V. M. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 15022-15032. D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 936-945; A. H. Roy, C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **2007**, *129*, 2082-2093; C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1997**, *119*, 3165-3166; I. F. D. Hyatt, H. K. Anderson, A. T. Morehead, A. L. Sargent, *Organometallics* **2008**, *27*, 135-147.

[5] R. Goikhman, D. Milstein, *Angew. Chem. Int. Ed.* **2001**, *40*, 1119.

[6] G. L. Moxham, H. Randell-Sly, S. K. Brayshaw, A. S. Weller, M. C. Willis, *Chem.-Eur. J.* **2008**, *14*, 8383-8397.G. L. Moxham, H. E. Randell-Sly, S. K. Brayshaw, R. L. Woodward, A. S. Weller, M. C. Willis, *Angew. Chem. Int. Ed.* **2006**, *45*, 7618-7622.

[7] I. Pernik, J. F. Hooper, A. B. Chaplin, A. S. Weller, M. C. Willis, *Acs Catalysis* **2012**, *2*, 2779-2786; bA. B. Chaplin, J. F. Hooper, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc.* **2012**, *134*, 4885-4897.

[8] F. Eisentrager, A. Gothlich, I. Gruber, H. Heiss, C. A. Kiener, C. Kruger, J. U. Notheis, F. Rominger, G. Scherhag, M. Schultz, B. F. Straub, M. A. O. Volland, P. Hofmann, *New J. Chem.* **2003**, *27*, 540-550.

[9] K. G. Kou, D. N. Le, V. M. Dong, *J. Am. Chem. Soc*. **2014**, *136*, 9471.

[10] A. H. Roy, C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc*. **2007**, *129*, 2082; R. J. Pawley, M. A. Huertos, G. C. Lloyd- Jones, A. S. Weller, M. C. Willis, *Organometallics* **2012,** *31*, 5650.

[11] P. Nägele, U. Herrlich, F. Rominger, P. Hofmann. *Organometallics* **2013**, *32,* 181−191.