Rapid screening and combinatorial methods in homogeneous organometallic catalysis*

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Abstract: Methods are discussed for rapid screening of soluble and polymer-bound homogeneous catalysts for activity. A polymer-bound phosphine library is synthesized, and a modular tridentate pincer CNC bis-carbene Pd complex is described. The possibility of C-bound His in metalloenzymes is raised.

Homogeneous catalysis has much to offer Green Chemistry. By allowing reactions to occur at lower temperature and pressure, energy is saved. By enhancing selectivity, waste is avoided. Waste can even be essentially eliminated if catalysis allows atom-economic processes to be used. These are reactions like eq. 1 in which all the atoms of the reagents are incorporated into the product [1,2]. This particular rhodium-catalyzed reaction—the Monsanto Process—is a commercially important route to acetic acid [3]. In contrast, much conventional industrial chemistry still goes via reactions that produce stoichiometric amounts of inorganic salts or tainted water as byproducts.

$$MeOH + CO = MeCOOH \qquad (1)$$

For each new application, new homogeneous catalysts may well need to be identified and optimized, then understood mechanistically. Mechanization and computerization, now becoming more readily available and efficient, can help with all these goals. Combinatorial chemistry [4–7], together with rapid catalyst screening [8,9], has potential value in identification and optimization. The latest methods of computational and theoretical chemistry can give very valuable mechanistic information in ruling out otherwise plausible pathways and predicting structural information for transient species and transition states [10]. Here, we naturally discuss only the title topic, although by doing so we do not intend to detract from the importance of mechanistic understanding.

The principles of combinatorial chemistry have been covered in several recent monographs and reviews [11–16]. In summary, the concept involves creating a large number of chemically distinct species—called a library—in a controlled way. This library is then assayed by a suitable rapid screening protocol to see if a desired response is elicited. The library members showing a good response, termed "hits", are then analyzed to determine the chemical structure responsible for the desired response.

The field has its intellectual roots in an understanding of how the immune system works and in Merrifield's [17] approach to polypeptide synthesis. The immune system has the task of tagging foreign biomolecules to label them for attack. To do this, it creates a library of polypeptides of variable structure, then senses when one of these peptides by chance binds strongly to a foreign target, such as the surface of an invading bacterium, for example. The successful immune system peptide is then synthesized on a large scale to carry out its defense role in the body.

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Merrifield's polypeptide synthesis involves covalently attaching a cleavable linker group to the chloromethyl group of a chloromethylated polystyrene (Merrifield's resin). A polypeptide is then synthesized by attaching a series of the appropriate amino acids one-by-one using a coupling reagent to form the new peptide bonds. A key advantage is the simple isolation procedure that consists of filtering the beads from the reaction mixture. Once the desired primary structure is formed, the polypeptide is liberated by cleavage at the linker [15].

With this synthesis in place, it became possible to create a library of polypeptides by keeping certain residues fixed and varying the groups present at other positions. Suppose that all 20 common amino acids were incorporated at one variable position in the chain, the library would consist of a total of 20 members. The number of peptides increases very dramatically as we move to two, three, and four variable positions: these choices give 8000, 160 000, and 3.2×10^6 members, at least theoretically speaking. We leave aside the problem of deconvoluting the library to determine which member was responsible for any hit, but these issues are discussed in the literature [4–7,11–16].

Ellman [18] made an important step forward in applying combinatorial ideas to organic chemistry by synthesizing a library of benzodiazepines, looking for pharmacological activity. Indeed, this type of approach is now widely used in bioorganic and medicinal chemistry.

How have catalysts been discovered up to now? A typical example is our own early work on $[Ir(cod)(PCy_3)(py)]PF_6$ (**1**, py = pyridine), sometimes called Crabtree's catalyst [19]. Equipped with Togni's [20] asymmetric ferrocene ligand, this type of hydrogenation catalyst has proved useful for the industrial asymmetric synthesis of the agrochemical, (S)-metolachlor [21]. Inspired by Shrock and Osborn's earlier work [22], mainly on rhodium, Hugh Felkin, George Morris, and I examined about a dozen different iridium compounds over two years with the result that **1** was identified as the best member of the series. Not only was synthesis and characterization of each potential catalyst time-consuming, but the then-preferred solvent for hydrogenation, methanol, gave an inactive catalyst; a noncoordinating solvent, dichloromethane, that had not been generally useful for prior catalysts, was required for activity. Not just **1** but all current homogeneous catalysts have been discovered by traditional methods, but a new approach using combinatorial ideas seems to offer promise for the future.

How do we envisage application of these ideas to organometallic catalyst discovery? The simplest case would be use of an appropriate chemical sensor in a rapid parallel assay to detect rate and perhaps also selectivity in a catalyst library of conventional homogeneous catalysts. This would allow desirable catalysts to be identified rapidly from a large set. In the next phase of the evolution of the field, parallel synthesis is expected to allow access to a diverse library of ligands to which a variety of metals could be coordinated before assay. Peptide-based ligands have been made in parallel using established peptide coupling techniques [23–27], but when we move to more traditional organometallic ligands, parallel synthetic methods are still in the early stages of development. Here, the synthesis of the catalysts becomes the rate-determining step, and we do not expect to be able to fully capitalize on the efficiency of the rapid assay. In cases where a catalyst is formed from self-assembly of simple, preferably commercially available, reagents, however, the synthesis of the catalyst is avoided, and the rapid screening approach is expected to have distinct advantages. If advances can be made along these lines, it is likely that interest will shift from traditional ligands that are hard to synthesize in parallel, to ligand types that lend themselves more readily to this approach. Appropriate ligands are expected to be modular, in the sense of having several separately variable elements, diverse, in the sense of encompassing a wide range of electron donor/acceptor character and steric complexity, as well as being readily synthesized by high-yield procedures.

Discussions with colleagues have indicated that there is often a misunderstanding about the scientific basis of these ideas. Some consider that in applying them, we would be abandoning the reasoned approach that has worked well in the past and become a hostage to the vagaries of chance. In fact, a classical scientific experiment can be designed, executed, and interpreted well or badly, just like a combinatorial experiment. In the latter case, as in the former, we start with a hypothesis about where activity might be expected, we design our methods to test these ideas, and we interpret the results with care.

Of course, care needs to be taken and data must not be overinterpreted, but if we maintain traditional scientific standards, we can expect useful data with a considerable gain in efficiency. The groundwork needs to be laid carefully because the necessary methods do not exist and we lack a generally accepted framework in which to design and interpret experiments.

The first step in this direction must be the development of suitable sensors for detecting progress in the catalytic reaction in some way. Consider the schematic catalytic reaction of eq. 2, where we can in principle look for a sensor that detects disappearance of A or B or formation of C or D or heat production. Production of heat is unsatisfactory except where one reaction alone can occur, such as in ester hydrolysis. Heat production would be a misleading indicator in partial oxidation, for example, because undesired total oxidation would produce more heat. Disappearance of starting material is a possibility, but this approach tells us nothing about selectivity, often a key property for optimization in homogeneous catalysis. The best situation would be detection of the desired product. Many different approaches have been reported to address this problem. Methods such as GC [23,26,28,29], GLC [27], HPLC [30–32], UV/Vis [33,34], electrospray ionization MS [35,36], IR thermography [37,38], fluorescence [39], and visible color change [40,41] have been used to assay for product formation.

$$A + B = C + D + heat \qquad (2)$$

Other more elaborate methods can be expected in the future, for example real-time spectroscopic sampling of the reaction vessels by *in situ* IR with computer analysis of the data. In our initial work, however, we wanted to keep the systems as simple as possible in order to build up understanding of how to design and analyze experiments of this sort and where problems can be expected.

Since many reactions such as hydrogenation, hydroformylation, and hydrosilation involve saturation of C=C double bonds [42], we decided to develop a C=C sensor for catalyst screening. Thinking that a visible light response might be appropriate for the initial work, we designed a reactive visible dye [43,44]. Conventional dyes consist of an electron donor linked to an electron-acceptor by an unreactive unsaturated link. We thought that replacing the link by a C=C or C=N bond would give us a dye that would bleach on saturation of the C=X link. We felt we also needed to replace potentially ligating Me_2N groups and potentially reactive NO_2 groups of conventional dyes by groups with no accessible functionality. That reasoning led us to dyes **2a–b**, where the donor is ferrocenyl and the acceptor is a pyridinium ion; the C=X bond can be C=C (**2a**) or C=N (**2b**). The quaternized pyridinium was chosen with the intention of attaching the dye to Merrifield resin or another chloromethyl functionalized surface. The benzyl group attached to the pyridine ring in **2** was chosen to enhance the solubility.

2a X = CH
2b X = N
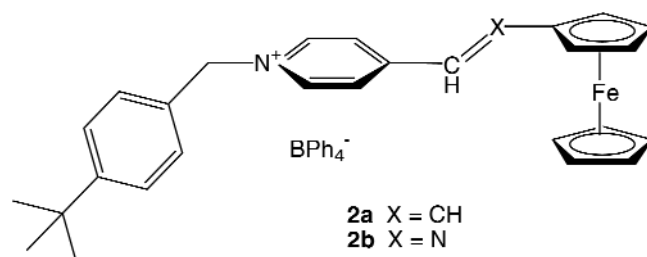
The intense colors of the dyes (**2a**, deep purple; **2b**, dark blue) are reflected in their high extinction coefficients (**2a**, 12 600 M^{-1} cm^{-1}; **2b**, 5200 M^{-1} cm^{-1}). On saturation of the C=X bond, the color is bleached to a light straw shade; for example, the hydrogenated complexes, **3a–b**, have quite low extinction coefficients (**3a**, 1900 M^{-1} cm^{-1}; **3b**, 2000 M^{-1} cm^{-1}). The dyes can be used in a visual test for catalytic activity. To simplify the system by avoiding gas handling problems, we decided to look at hydrosilation instead of hydrogenation. Accordingly, reaction and control lanes of 1 mL mini-reactors were prepared by drilling wells in a teflon block and loaded with dyes **2a** or **2b** and one of twelve poten-

tial catalysts. After addition of Ph_2SiH_2 to the reaction lane, the block was monitored visually and with a digital camera. Two times, t_i and t_f, were found to be useful. The first corresponds to the time after which the first apparent bleaching is observed and the second to the time after which no further change is apparent. These times proved to correspond to ca. 40 and 95% consumption of the dye, respectively. Wilkinson's complex [45], a well-known catalyst, was found to be among the best, but a palladium complex (**4**) [46] not previously known to catalyze this reaction was also found to be extremely active.


R = *o*-tolyl

4
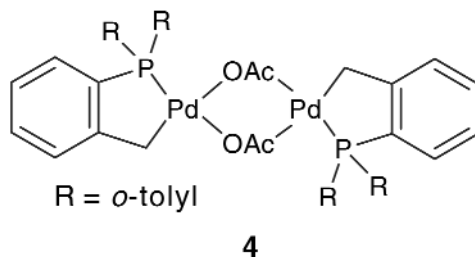
Disappearance of starting material does not necessarily mean appearance of the desired product. Indeed, closer study has shown that the product of the "hydrosilation" reaction of **2a** is mainly the hydrogenation product, **3a**. Conventional alkenes normally give very little hydrogenation product under these conditions [47] so the abnormal electronic character of the C=C bond in **2a** makes it a nonstandard substrate; it also reacts about a factor of 10^3 faster than a typical alkene such as stilbene, again nonstandard. The C=C bond is apparently polarized so that, unlike normal alkenes, it can be attacked by $NaBH_4$; such polarization could help explain the faster rate of the catalytic reactions. The color also proved to be significantly affected by ion pairing (dependence on counterion) and by the solvent (solvatochromism). Finally, visible light irradiation led to initial *trans*/*cis* isomerism, causing the color to fade somewhat, and, after prolonged irradiation, to decomposition of the dye.

This complex behavior pattern led us to move to more standard substrates as sensors. In doing so, we had to move from visible dyes to fluorescent sensors. A good opportunity was presented by alkyne metathesis [42]. The well-known Schrock catalyst, $(tBuO)_3W≡CtBu$ [48], for alkyne metathesis is not really satisfactory for a combinatorial approach because it is made by traditional organometallic synthesis and is very air- and water-sensitive. Instead, we moved to a catalyst system first described by Mortreux [49] and later elaborated upon by Mori [50] and Bunz [51], which consists of $W(CO)_6$ and ArOH. Being self-assembling from commercial precursors and easily modular, this catalyst is easy to adapt for combinatorial studies.

We decided to look at $ArC≡C(n\text{-}Pr)$ (Ar = naphthyl), where the expected products would be fluorescent $ArC≡CAr$ and volatile $(n\text{-}Pr)C≡C(n\text{-}Pr)$. The synthesis of $ArC≡C(n\text{-}Pr)$ involved the Sonogashira coupling [52] of 2-bromonaphthalene and 1-pentyne. Trace amounts of Pd used in the coupling are present in $ArC≡C(n\text{-}Pr)$ even after column chromatography. Further purification by vacuum distillation causes reaction of $ArC≡C(n\text{-}Pr)$ with the trace Pd at the high temperature needed for distillation. Fluorescence is a very sensitive technique that can easily be altered by trace amounts of impurity. For this reason, even though the formation of $ArC≡CAr$ could be confirmed by ^{1}H NMR and GC-MS, the observed fluorescence was not consistent.

The majority of organometallic homogeneous catalysts that we and others have worked with over the years contain phosphine ligands. Our next step was to try to use combinatorial synthesis to prepare a library of phosphine ligands on poly(styrene-*co*-divinylbenzene). The route, shown in Fig. 1, involves attaching a bromophenyl linker that is subsequently substituted by reaction with *t*BuLi followed by $RPCl_2$. Another R group can be installed by reaction with an organolithium or magnesium reagent. The same procedure carried out on a cleavable version of the same system (Fig. 2) gave the result that the phosphine was >95% the desired species (^{1}H and ^{31}P NMR, IR) [53].
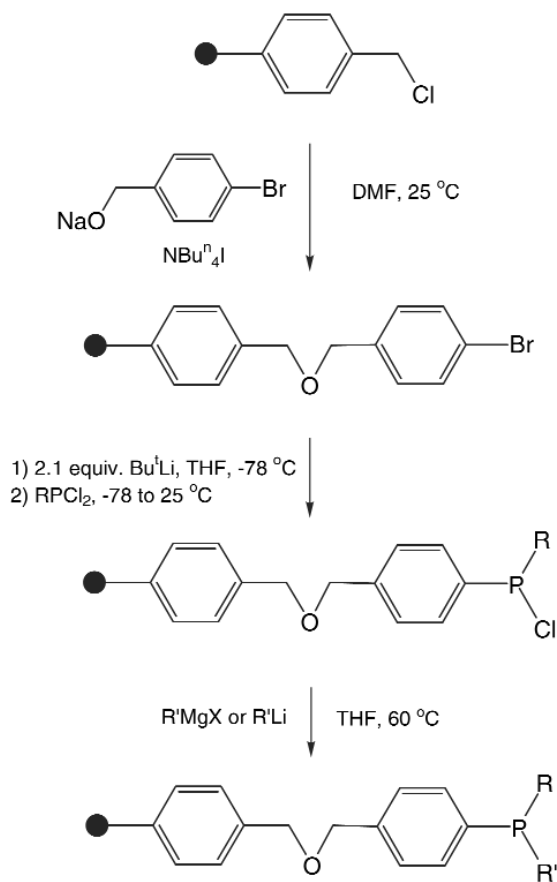
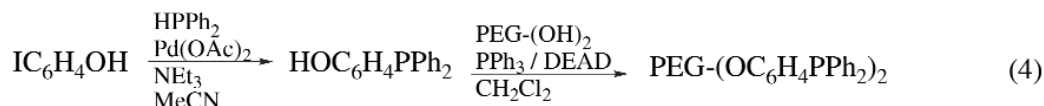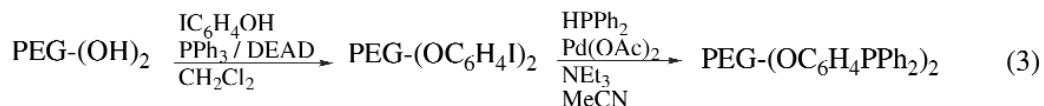**Fig. 1** Generalized synthesis of the phosphine library on poly(styrene-*co*-divinylbenzene).
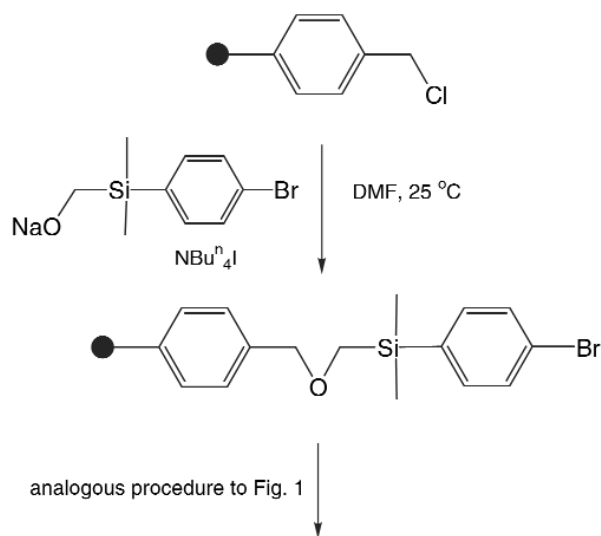
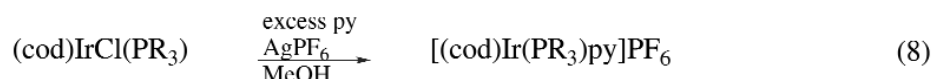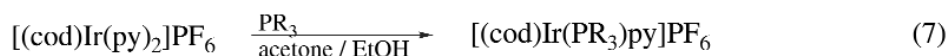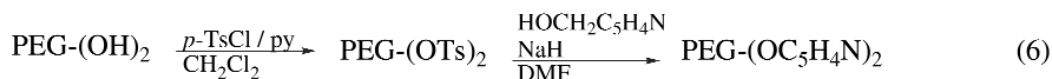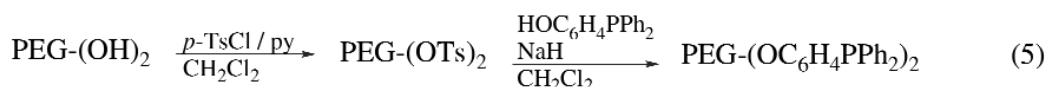**Fig. 2** Synthesis of cleavable bromophenyl linker.

The library consists of a set of vials each of which contains only beads that all contain the same ligand, so that each ligand can be run separately and hits can be readily identified without deconvolution methods. The beads can be readily loaded with metal by exposing them to $[M(cod)(py)_2]PF_6$, where M = Ir or Rh. Catalytic data can be obtained from the resulting beads using the alkene dye assay and Ph_2SiH_2 as the co-reagent as before. Unfortunately, the data are not reliable, because the loading of the metal on the beads is not reliable. Loading was determined by ICP analysis [54]. Even the control beads containing a blind linker lacking the Br substituent bind metal and show some activity. We believe that the phosphine group is correctly introduced at the cleavable linker sites but that the lithium reagents also cause lithiation of reactive polymer sites such as free vinyl groups so that phosphorus groups also get attached elsewhere than intended. While these sites are not cleavable, they still affect activity in an on-bead assay. This makes it clear that on-bead assay for catalytic activity may not be reliable and the catalyst may not be single-site. In addition, on-bead assay is likely to be affected by mass transport of substrate into the bead and by the differential swelling caused by different solvents being used. This limits the utility of the Merrifield type of approach for phosphines. In spite of these difficulties, our data showed that the Ar-P(Ph)(1-naphthyl) bead-bound ligand had the best activity with Ir as the metal loaded and that a soluble version of the Ir catalyst was also active.

In view of the difficulties mentioned, we decided not to pursue this approach but to shift to a soluble polymer where the advantages of simple recovery of the polymer would still apply but where the polymer-bound catalyst was sufficiently soluble in typical solvents used in catalysis. This approach also has the significant advantage that the polymer-ligand and polymer-ligand-metal conjugate are both readily detectable by conventional solution NMR procedures, so we are able to obtain a direct indication of purity for quality control of the library. It is not yet clear how far degradation of library quality also degrades the reliability of the results, but it is clear that the purity has to be well determined so the data can be interpreted with the appropriate level of confidence.

Poly(ethylene)glycol [PEG, $HO(CH_2CH_2O)_nCH_2CH_2OH$] seemed to be most appropriate in having broad solubility in organic and even aqueous solvents but still being precipitated readily by Et_2O, for example [55a]. Since the iridium catalyst **1** contains both a phosphine and a pyridine ligand, we decided to prepare both PEG/phosphine and PEG/pyridine conjugates. The PPh_3 equivalent was used instead of PCy_3 because it also makes for an active catalyst and is less air sensitive. The grafting took place at each end of the polymer chain, so when we use the nomenclature, PEG-$(OH)_2$, we mean the starting diol, and PEG-$(OR)_2$ refers to derivatives with an R group at each end.

The synthetic routes shown in eqs. 3–8 were used to make the materials used. Equations 3–5 show methods used to make PEG-$(OC_6H_4PPh_2)_2$ and eq. 6 shows the synthesis of PEG-$(OCH_2C_5H_4N)_2$. The yield of polymer was generally 95%, and the efficiency of incorporation of the desired end groups and their homogeneity in the sample were both high, as judged by ^1H and ^{31}P NMR spectroscopy. Reaction with either $[(cod)Ir(py)_2]PF_6$ or $(cod)IrCl(PR_3)$ went smoothly to yield PEG-ligand-metal conjugates that gave ^1H NMR spectra in which every peak of the end-groups could be assigned by comparison with soluble compounds of analogous type. The analogous solution phase reactions are shown in eqs. 7 and 8. The polymer itself conveniently gives a single peak, albeit intense. The resulting PEG-ligand-metal conjugates were catalytically active for hydrogenation, as shown with allylbenzene as substrate. This species was chosen so isomerization could also be estimated for each catalyst [55b].

$$\text{PEG-}(OH)_2 \xrightarrow[\substack{PPh_3 / DEAD \\ CH_2Cl_2}]{IC_6H_4OH} \text{PEG-}(OC_6H_4I)_2 \xrightarrow[\substack{Pd(OAc)_2 \\ NEt_3 \\ MeCN}]{HPPh_2} \text{PEG-}(OC_6H_4PPh_2)_2 \qquad (3)$$

$$IC_6H_4OH \xrightarrow[\substack{Pd(OAc)_2 \\ NEt_3 \\ MeCN}]{HPPh_2} HOC_6H_4PPh_2 \xrightarrow[\substack{PPh_3 / DEAD \\ CH_2Cl_2}]{PEG-(OH)_2} \text{PEG-}(OC_6H_4PPh_2)_2 \qquad (4)$$

$$\text{PEG-(OH)}_2 \xrightarrow[\text{CH}_2\text{Cl}_2]{\textit{p}\text{-TsCl / py}} \text{PEG-(OTs)}_2 \xrightarrow[\substack{\text{NaH} \\ \text{CH}_2\text{Cl}_2}]{\text{HOC}_6\text{H}_4\text{PPh}_2} \text{PEG-(OC}_6\text{H}_4\text{PPh}_2)_2 \qquad (5)$$

$$\text{PEG-(OH)}_2 \xrightarrow[\text{CH}_2\text{Cl}_2]{\textit{p}\text{-TsCl / py}} \text{PEG-(OTs)}_2 \xrightarrow[\substack{\text{NaH} \\ \text{DMF}}]{\text{HOCH}_2\text{C}_5\text{H}_4\text{N}} \text{PEG-(OC}_5\text{H}_4\text{N})_2 \qquad (6)$$

$$[(\text{cod})\text{Ir(py)}_2]\text{PF}_6 \xrightarrow[\text{acetone / EtOH}]{\text{PR}_3} [(\text{cod})\text{Ir(PR}_3)\text{py}]\text{PF}_6 \qquad (7)$$

$$(\text{cod})\text{IrCl(PR}_3) \xrightarrow[\substack{\text{AgPF}_6 \\ \text{MeOH}}]{\text{excess py}} [(\text{cod})\text{Ir(PR}_3)\text{py}]\text{PF}_6 \qquad (8)$$

Particularly relevant to green chemistry was the observation that these catalysts are also effective in water/substrate two-phase media without the necessity for addition of an external phase transfer agent. Such solvent-free, two-phase systems avoid the need for volatile organic solvents, but normally require the presence of phase transfer catalysts. Very likely, PEG acts as its own phase transfer agent in this system. Unfortunately, precipitation of PEG from water can be a problem in the presence of salts. Future work on constructing a PEG-based library is anticipated.

Phosphines have been used for more than 30 years in a very wide range of homogeneous organometallic catalysts. Very recently *N*-heterocyclic carbenes [56] have been shown to have a phosphine-like ability to support catalysis by platinum group metals. Examples include carbene complexes used for C–C [57–60] and C–N [61,62] couplings and olefin metathesis [63–66]. They have the advantages of being readily synthesized and, if incorporated into chelating ligands, could readily be made modular, thus making them suitable for combinatorial/rapid screening work.
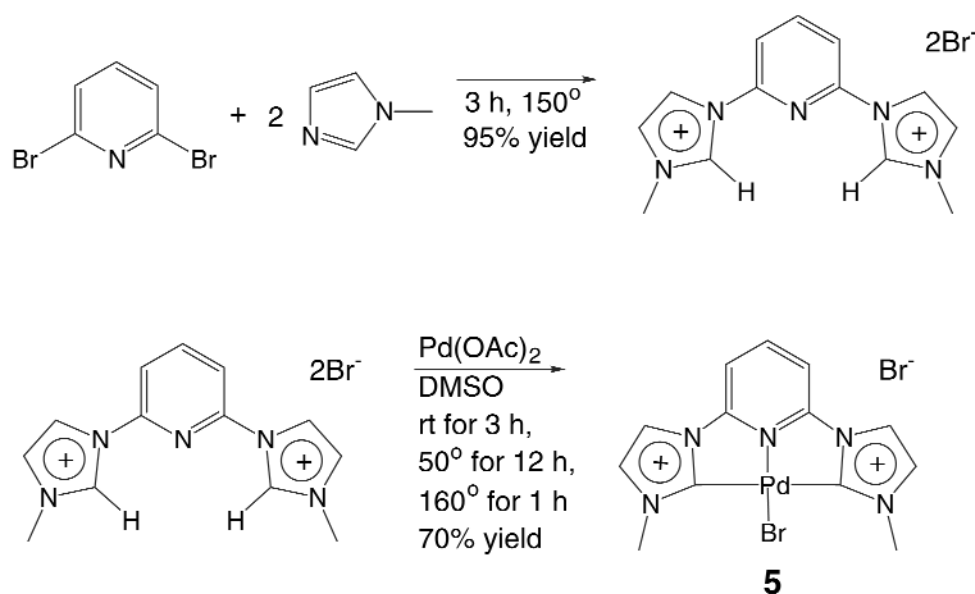

Fig. 3 Synthesis of tridentate pincer CNC bis-carbene Pd complex.

One other advantage such carbene ligands seem to have is thermal stability. This could be important for us because we have been particularly interested in alkane dehydrogenation reactions that tend to require elevated temperatures. These conditions commonly lead to partial decomposition of the phosphines employed. A typical decomposition route is P–C bond cleavage. In the case of $[IrH_2(tfa)\{PAr_3\}_2]$ (Ar = p-FC_6H_4) as catalyst, we were able to unambiguously demonstrate that catalyst activity decreases with the formation of the P–C bond cleavage product, C_6H_5F.

In order to further enhance the thermal stability of our ligand, we chose to incorporate it into a pincer ligand system. Pincer phosphines have been shown to be particularly thermally stable [67] and to mediate alkane dehydrogenation [68]. Figure 3 shows the general synthetic route of the ligand [69] and of the Pd(II) complex. The latter was chosen merely to assay activity in a simple reaction, Heck coupling. We are also moving on to the Ir, Rh, and Ru complexes where we feel we can extend the range of catalytic activities for hydrocarbon reactions. The pincer ligand seems to bind readily to a variety of metals to give single well-defined and soluble complexes. Solubility can be enhanced by using bulky R groups instead of methyl in the wingtip positions of the ligand. For example, n-butyl has proved useful in this respect. Even at this early stage, we have found very encouraging results in that catalyst **5** gives the Heck coupling of eq. 9 with a turnover frequency of 16 500 h^{-1} at 165 °C in dimethylacetamide (DMA). The catalyst is also active in air [70].

These carbene ligands are often considered to have electronic characteristics similar to those of phosphines. It is certainly the case that they seem well-suited to mediating catalytic reactions. This raises an interesting bioinorganic point. Histidine is a common ligand for metals in metalloenzymes, yet His is conventionally always considered as an exclusively N-donor ligand. If a C-donor version were accessible under certain circumstances, this might strongly alter the properties of the active site without any pronounced biophysical "signature" to call attention to the change. In particular, since C cannot normally be distinguished from N in a protein crystal structure, C-His groups may be present in a number of proteins or model compounds, but unrecognized. We are currently examining this possibility.

$$(9)$$
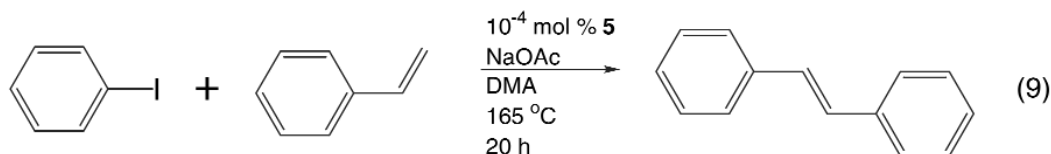
The facility with which these carbenes can be incorporated into chelating ligands and the ligands attached to metals suggests that they will gain in importance and more readily lend themselves to the combinatorial/rapid screening approach.

ACKNOWLEDGMENTS

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