DOI: 10.1002/ejoc.200500972

Beyond TPPTS: New Approaches to the Development of Efficient Palladium-Catalyzed Aqueous-Phase Cross-Coupling Reactions

Kevin H. Shaughnessy*[a]

Keywords: Biphasic catalysis / Palladium / Cross-coupling / Green chemistry

Water is an attractive solvent for metal-catalyzed reactions with both economic and environmental sustainability benefits. In addition, the use of a hydrophilic catalyst in an aqueous-biphasic solvent system provides the opportunity to easily recover, and potentially recycle, the catalyst species. The feasibility of cross-coupling reactions catalyzed by hydrophilic palladium catalysts was first demonstrated using sulfonated analogs of triphenylphosphane, such as tris(3-sulfonatophenyl)phosphane trisodium salt (TPPTS). Catalysts derived from TPPTS and other structurally similar hydrophilic phosphanes are generally effective only with aryl iodides and activated aryl bromides. This microreview will focus on more recently developed hydrophilic ligands with increased steric demand and electron-donating abilities that are effective in coupling reactions of aryl bromides and chlorides under mild conditions in aqueous solvents.

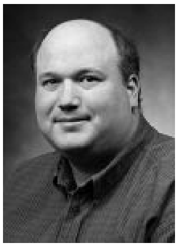
Introduction

Palladium-catalyzed cross-coupling reactions, such as the Heck,[1] Suzuki,[2,3] Stille,[4] Sonogashira,[5] and Hartwig–Buchwald (H-B)[6,7] couplings (Scheme 1), have become powerful tools for carbon–carbon and carbon–heteroatom bond formation in the synthetic chemist's arsenal.[8] These coupling reactions are highly versatile in the types of substrates that can be coupled, as well as being highly functional group tolerant. In the thirty years since the initial report of these reactions, there has been an extensive amount of effort devoted to developing ever more active, general, and long-lived catalysts. These coupling reactions are increasingly being applied in the manufacture of fine chemicals and pharmaceuticals, although the catalyst activity and separation continue to be hurdles to implementation.[9–11]

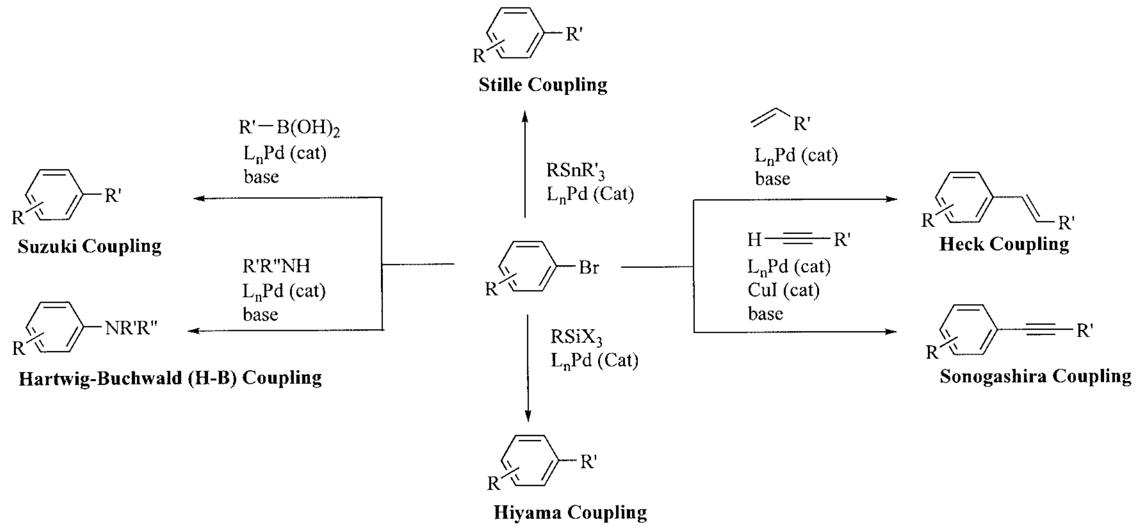
Increasing environmental awareness as well as challenges encountered in the use of homogeneous metal catalysts in industrial settings has led to an increasing interest in the use of alternative solvents.[12,13] Water is an attractive alternative to traditional organic solvents because it is inexpensive, nonflammable, nontoxic, and environmentally sustainable. In the fine chemical industries where relatively large amounts of waste are generated per kilogram of product,[14,15] the bulk of which is solvent waste,[16] increased use of water could have significant benefits. In addition, the use of water as part of a biphasic solvent system can simplify the separation of homogeneous catalysts from organic product streams, provided a hydrophilic catalyst is used. The removal of residual palladium is a significant issue in the application of cross coupling in pharmaceutical synthesis.[10]

---

[a] Department of Chemistry and the Center for Green Manufacturing, The University of Alabama,
Box 870336, Tuscaloosa, AL 35487-0336, USA
Fax: +1-205-348-4435
E-mail: kshaughn@bama.ua.edu



Kevin H. Shaughnessy was born in 1970 and raised in Trumbull, Nebraska. He earned his B.S. degree with honors and highest distinction from the University of Nebraska-Lincoln in 1992, where he worked with Reuben D. Rieke. He then joined the group of Robert M. Waymouth at Stanford University, where he developed zirconocene-catalyzed carbometalation reactions. Upon completing his PhD (1998), he moved to Yale to work with John F. Hartwig on palladium-catalyzed enolate arylations and development of high-throughput screening assays. In 1999, he joined the chemistry faculty at the University of Alabama, where he is currently an Associate Professor of Chemistry. His research interests have focused on the development of catalytic methodologies in alternative solvents and understanding how these solvents affect fundamental organometallic reactivity.



Scheme 1. Commonly used examples of palladium-catalyzed cross-coupling reactions.

Casalnuovo[17] was the first to demonstrate that a variety of palladium-catalyzed cross-coupling reactions could be carried out in predominately aqueous solvents using the hydrophilic catalyst, $(TPPMS)_3Pd$ [TPPMS = diphenyl(3-sulfonatophenyl)phosphane, Figure 1]. In the 15 years since Casalnuovo's report, a large variety of hydrophilic phosphane ligands have been synthesized and applied to cross-coupling reactions. Nearly all of these ligands are based on the triphenylphosphane core.[18–23] Several reviews describe the application of these and many related hydrophilic triarylphosphanes in palladium-catalyzed cross couplings.[13,24–29]

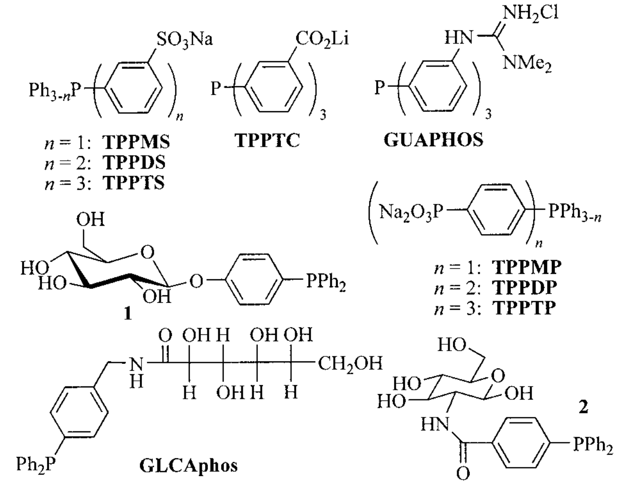
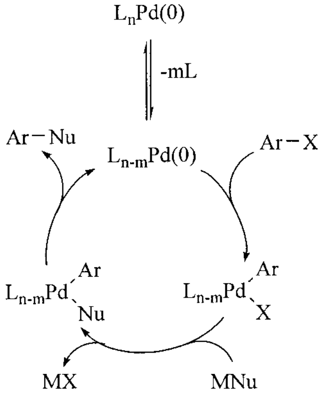


Figure 1. Representative examples of hydrophilic triarylphosphanes applied to aqueous-phase Pd-catalyzed coupling reactions.

Increased catalyst activity and wider substrate generality are the major goals driving the development of new cross-coupling catalyst systems. Researchers continue to seek catalysts and reaction conditions that will provide high catalyst turnover numbers (TON) and frequencies (TOF) in an effort to reduce the amount of catalyst required for a given reaction. Over the past decade there has been a growing effort to widen the scope of organic electrophiles that can be used under mild conditions to include aryl chlorides,[30] aryl tosylates,[31–33] benzoic acid derivatives,[34] and aliphatic halides.[35]

Aryl chlorides, in particular, have attracted much attention, as they are generally more available and significantly less expensive on an industrial scale than aryl bromides or iodides. In addition, they generate less halide waste by weight than bromides or iodides. Unfortunately, aryl chlorides are much less reactive in cross-coupling reactions than aryl bromides or iodides. The reactivity of aryl halides to oxidative addition, the first and often rate-determining step of the catalytic cycle (Scheme 2), follows the trend ArI > ArBr > ArCl >> ArF. This trend corresponds to the C–X bond strength. For example, iodobenzene undergoes oxidative addition to $[Pd(PPh_3)_4]$ at room temperature, bromobenzene is activated at 80 °C, and chlorobenzene reacts slowly at 135 °C.[36]



MNu	Reaction Class
RBX_2	Suzuki
$RSnR'_3$	Stille
$RSiR'_3$	Hiyama
RZnX	Negishi
RMgX	Kumada
RR'NH	H-B
ROH	H-B
RSH	H-B
$RC(O)CHR'_2$	H-B

Scheme 2. General catalytic cycle for Pd-catalyzed cross-coupling reactions.

Sterically demanding, strongly electron-donating ligands are generally required to activate less reactive substrates, such as aryl chlorides. Examples of sterically demanding, electron-rich ligands that have been applied to coupling of aryl chlorides include bulky trialkylphosphanes (Figure 2), (**3** and **4**),[37–41] aryldialkylphosphanes (**5** and **6**),[42–45] bicyclic triaminophosphanes (**7**), and N-heterocyclic carbenes (**8**).[46–48] The electron-rich palladium complexes formed from these ligands are better able to oxidatively add less reactive aryl chloride substrates under mild conditions. The increased steric demand is necessary to promote dissociation of a ligand from the L_2Pd^0 resting state, which is necessary prior to oxidative addition (Scheme 2).[49]

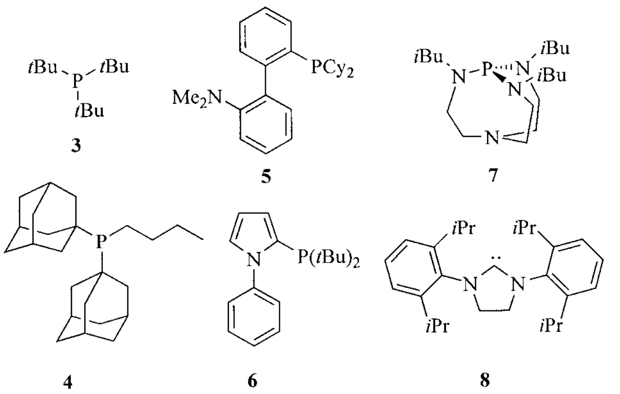


Figure 2. Examples of ligands applied to Pd-catalyzed cross-coupling reactions of aryl chlorides.

Until recently, the design of hydrophilic ligands for aqueous-phase cross-coupling reactions had focused almost exclusively on triarylphosphanes, such as the examples shown in Figure 1. While these ligands give synthetically useful systems for coupling of aryl iodides, they often show limited activity towards nonactivated aryl bromides and chlorides. There have been a few examples of aqueous-phase Suzuki coupling of aryl chlorides at elevated temperatures using ligand-free catalyst systems.[50–52] Suzuki couplings with aryl chlorides have also been reported with a nickel/TPPTS system using high catalyst loadings in water.[53] Until recently, little effort has been devoted to develop sterically demanding, electron rich, hydrophilic ligands in analogy to the types of ligands shown in Figure 2. This microreview will focus on hydrophilic ligands that are more sterically demanding and electron rich than TPPTS-like ligands. Catalysts derived from these ligands efficiently activate aryl bromides and chlorides under mild conditions in aqueous solvents.

Sterically Demanding Triarylphosphanes

One approach to altering the steric properties of TPPTS would be to add *ortho* substituents to the aromatic ring resulting in a more sterically hindered ligand. The sulfonation of tris(2,4-xylyl)phosphane gives the trisulfonated TXPTS ligand (Figure 3).[54,55] Incorporation of the electron-releasing methyl groups activates the arylphosphane to sulfonation, allowing the reaction to occur under milder conditions and with less oxidation of the phosphorus center than occurs in the sulfonation of triphenylphosphane. TMAPTS can be prepared in a similar manner from tris(4-methoxy-2-methylphenyl)phosphane.[56]

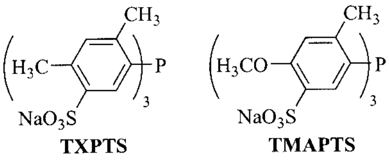
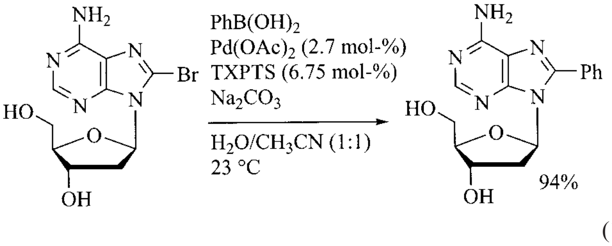


Figure 3. Sterically demanding sulfonated triarylphosphanes.

As expected, the addition of an *ortho*-methyl group greatly increases the cone angle of the ligands. The crystallographically determined cone angles for TPPTS are between 152° and 166°, while those for TXPTS range from 196° to 210°.[57] The cone angles determined from calculated geometries (DFT, local density approximation) and the STERIC program[58] were 155° for TPPTS, 210° for TXPTS, and 194° for TMAPTS.[59] The CO stretching frequency of *trans*-$[L_2Rh(CO)Cl]$ complexes, where L = TPPTS, TXPTS, and TMAPTS, were all determined to be $1992\,cm^{-1}$. Thus, all three ligands have similar electron-donating abilities, despite the presence of electron-releasing groups on the aromatic rings of TXPTS and TMAPTS. The sulfonated ligands are less electron-donating than triphenylphosphane ($\tilde{\nu}_{CO} = 1978\,cm^{-1}$) due to the electron-withdrawing sulfonate group, which appears to dominate the electronic nature of these ligands.

TXPTS with $Pd(OAc)_2$ gave a more active catalyst for Suzuki and Heck couplings of aryl bromides in aqueous solvents than did TPPTS.[56] In the Heck coupling of 4-bromotoluene with styrene in 50% aqueous acetonitrile, the TXPTS catalyst system gave a 77% yield after 2 hours at 80 °C, while the catalyst derived from TPPTS had only produced a 30% yield of the stilbene product under the same conditions. TMAPTS gave a similar conversion to product as the TPPTS system. The TXPTS/$Pd(OAc)_2$ system has also been applied to the Suzuki coupling of halonucleosides. TXPTS gave more active catalysts than TPPTS for the coupling of halopurine and halopyrimidine nucleosides.[60] Good to excellent yields of 8-aryl-2′-deoxyadenosine products were obtained at room temperature in the coupling of 8-bromo-2′-deoxyadenosine with phenylboronic acid using the TXPTS/$Pd(OAc)_2$ system [Equation (1)]. The TXPTS catalyst system was also less prone to inhibition by guanine in these reactions than the TPPTS system, although the reason for this difference is not clear.[61]



(1)

Dialkylphosphinous Acids

Phosphinous acids have been found to be effective ligands for a wide range of palladium-catalyzed cross-coupling reactions of aryl chlorides and bromides.[62,63] Under the basic conditions typical of these cross-coupling reactions, these ligands are deprotonated to give anionic phosphinites. Wolf and co-workers have shown that phosphinous acid/Pd catalyst systems can be used for the aqueous-phase Stille,[64] Sonogashira,[65] and Hiyama[66,67] couplings of activated aryl bromides and chlorides in aqueous solvents at high temperatures (135–140 °C). Nonactivated aryl chlorides gave modest yields under these conditions. The POPd catalyst gave optimal activity for the Stille and Sonogashira couplings, while POPd1 was the preferred catalyst for the Hiyama coupling (Figure 4). The POPd catalyst system could be used for four reaction cycles in the Stille coupling of phenyltrimethylstannane and 3-bromopyridine. Over the four cycles, the yield slowly decreased from 96% for the first cycle to 84% for the final one.

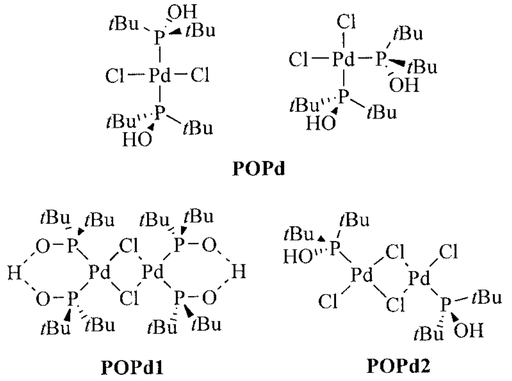
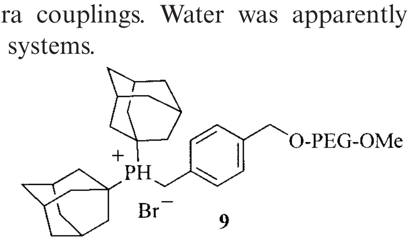


Figure 4. Phosphinous acid complexes of palladium.

Sterically Demanding Trialkylphosphanes

Catalytic Applications: Plenio[68,69] has reported a PEG-supported diadamantyl(benzyl)phosphonium salt (Figure 5, **9**) that provided effective catalysts for the Sonogashira and Suzuki coupling of aryl bromides and chlorides in a biphasic DMSO/heptane solvent system. The PEG-supported ligand **9** gave an effective and recyclable catalyst system for the Sonogashira coupling of both activated and deactivated aryl bromides at 60 °C. In most cases, the catalyst system could be used for five cycles, with an overall yield >90%. The **9**/Pd system gave good yields (>90%) for the Suzuki coupling of aryl chlorides over six cycles with both activated and deactivated aryl chlorides. DMSO was found to be the optimal solvent for both the Suzuki and Sonogashira couplings. Water was apparently not tested with these systems.

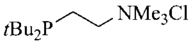


9

Figure 5. PEG-modified diadamantylphosphonium salt.

When we began our studies we were interested in preparing hydrophilic ligands with similar electronic and steric properties to $t\mathrm{Bu}_3\mathrm{P}$. We were inspired to prepare *t*Bu-Pip-phos and *t*Bu-Amphos by the Cy-Pip-phos ligand reported by the Grubbs group (Figure 6).[70] The ability of these ligands to give active cross-coupling catalysts was initially tested in a model Suzuki coupling of a nonactivated aryl bromide, 4-bromotoluene, at room temperature in 50% aqueous acetonitrile.[71] Under these conditions, TPPTS gave an inactive catalyst. In contrast, *t*Bu-Amphos and *t*Bu-Pip-phos in combination with $\mathrm{Pd(OAc)_2}$ (0.5 mol-%, 1:1 L/Pd) gave complete conversion to the product after 1 hour. The catalyst derived from Cy-Pip-phos gave a lower level of conversion (46%) under the same conditions. Catalysts derived from *t*Bu-Amphos or *t*Bu-Pip-phos gave complete conversion at room temperature with catalyst loadings as low as 0.01 mol-%. At 80 °C, complete conversion was achieved with a catalyst loading of 0.001 mol-%.

Cy-Pip-phos **tBu-Pip-phos**



tBu-Amphos

Figure 6. Hydrophilic, sterically demanding trialkylphosphanes.

Catalysts derived from *t*Bu-Amphos and *t*Bu-Pip-phos show similar activity in the Suzuki coupling of aryl bromides. Excellent yields of the coupled products were obtained at room temperature with both hydrophobic and hydrophilic aryl halides in water, water/acetonitrile, and water/toluene solvent systems.[72] Both catalyst systems show only moderate activity towards the Suzuki coupling of aryl chlorides, but higher yields were obtained with *t*Bu-Pip-phos (92%) than *t*Bu-Amphos (62%) in the phenylation of 4-chlorobenzonitrile, an activated aryl chloride, at 80 °C using 4 mol-% Pd. Only modest yields were obtained with both catalyst systems with 4-chlorotoluene and 4-chloroanisole (<30%), however.

The *t*Bu-Amphos catalyst system has been shown to give significantly more active catalysts for the Sonogashira and Heck couplings of aryl bromides in aqueous solvents than TPPTS.[72] In the Sonogashira coupling of 4-bromotoluene and phenylacetylene, the *t*Bu-Amphos/$\mathrm{Pd(OAc)_2}$ (2.5 mol-%) catalyst system gave a 91% yield after 5 h at 50 °C in 50% aqueous acetonitrile, while only a 30% yield was obtained with the catalyst derived from TPPTS after the same time. Good to excellent yields were obtained in the coupling of a range aryl bromides with aryl and alkyl acetylenes. In the Heck coupling, the *t*Bu-Amphos catalyst system (2.5 mol-%) gave a 74% yield in the coupling of 4-bromotoluene styrene at 80 °C after 5 hours, while the TPPTS/$\mathrm{Pd(OAc)_2}$-derived catalysts gave only a 14% yield under identical conditions. Catalysts derived from *t*Bu-Amphos gave similar activity and yields for the Heck coupling of aryl bromides as those derived from TXPTS.[56] The *t*Bu-

Amphos catalyst system gave low conversions in attempted Heck and Sonogashira couplings of nonactivated aryl chlorides.

A major advantage of using a water-soluble catalyst system is the ability to remove the homogeneous catalyst from the organic product stream by simple decantation and the potential to recycle the aqueous catalyst phase. No evidence of leaching of palladium from the *t*Bu-Amphos/Pd(OAc)$_2$ catalyst system was observed (<1 ppm contamination) in the crude product obtained from a Suzuki coupling in a water/toluene biphasic solvent system.[72] In addition, ^{31}P NMR spectroscopic analysis of the aqueous-phase showed that the catalyst resting state was the major phosphorus species in the aqueous solution. The aqueous phase could be used for three cycles of the room temperature Suzuki coupling of 4-bromotoluene, with > 84% yield for each cycle, before beginning to lose activity.

Steric and Electronic Properties and Coordination Chemistry: The steric and electronic parameters were determined for Cy-Pip-phos, *t*Bu-Pip-phos, and *t*Bu-Amphos in order to better understand their effects on catalyst systems (Table 1).[73] Cone angles (θ)[74] were determined from calculated structures (DFT, local density approximation) using the STERIC[58] program. Interestingly, *t*Bu-Amphos had a larger cone angle than *t*Bu$_3$P, despite the fact that a *tert*-butyl group in *t*Bu$_3$P was replaced with a primary alkyl chain. The increased cone angle for *t*Bu-Amphos can be explained by the fact that the primary alkylammonium chain projects the –NMe$_3$ towards the metal, resulting in a larger cone angle (Figure 7). The increasing cone angle correlated closely with the increasing activity of the catalysts derived from *t*Bu-Amphos, *t*Bu-Pip-phos, and Cy-Pip-phos for Suzuki coupling of aryl bromides at room temperature. In contrast, the electronic parameter (χ)[75] obtained from the A$_1$ CO stretching frequency of (R$_3$P)Ni(CO)$_3$ complexes did not correlate with catalyst activity for couplings of aryl bromides. Cy-Pip-phos had an intermediate χ value, yet gave the least effective catalyst. The χ parameter did appear to be more significant in the coupling of aryl chlorides, where the more electron rich, but smaller, *t*Bu-Pip-phos gave a more effective catalyst than *t*Bu-Amphos.

Table 1. Steric and electronic parameters for hydrophilic trialkylphosphanes.

Ligand	θ [°][a]	χ [cm^{-1}][b]
*t*Bu$_3$P	190	0.0
*t*Bu-Amphos	194	7.5
*t*Bu-Pip-phos	191	4.2
Cy-Pip-phos	186	5.8

[a] Cone angles from DFT (local density approximation) optimized structures using the STERIC program.[58] [b] Tolman electronic parameter. $\chi = \nu_{CO}[(R_3P)Ni(CO)_3] - \nu_{CO}[(tBu_3P)Ni(CO)_3]$.

The coordination chemistry of these ligands was also affected by the steric demand of the phosphanes. Complexation of *t*Bu-Amphos or *t*Bu-Pip-phos with Pd(OAc)$_2$ under reducing conditions (phenylboronic acid/base or sodium formate) resulted in the rapid formation of the L$_2$Pd^0 complex, which is presumed to be the active catalyst resting state (Scheme 2).[73] This complex was formed rapidly independent of the initial L/Pd ratio. In contrast, when the smaller Cy-Pip-phos ligand was used, the rate of formation of the L$_2$Pd^0 complex was inversely proportional to the phosphane concentration. At L/Pd ratios $\geq$ 2:1, *trans*-[L$_2$PdCl$_2$] was observed as an intermediate prior to reduction to the Pd^0 complex. Presumably reduction requires dissociation of a phosphane resulting in the inverse dependence on phosphane concentration. The larger *t*Bu-Amphos and *t*Bu-Pip-phos ligands do not form coordinatively saturated *trans*-[L$_2$PdCl$_2$] complexes. As a result, the reduction is not dependent on the phosphane concentration.

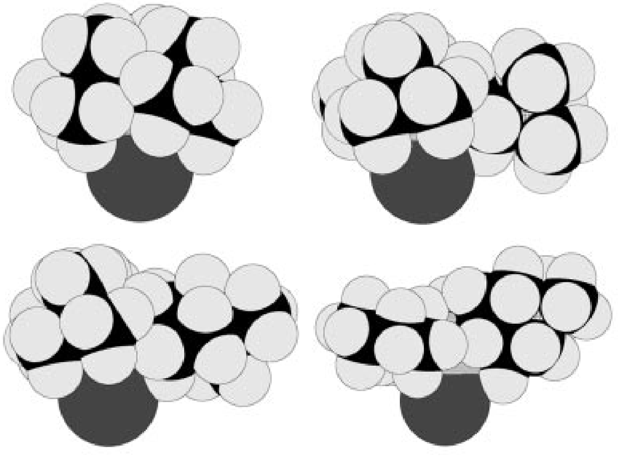


Figure 7. Space filling structures of DFT-optimized geometries for LPd^0 complexes. Upper left: (*t*Bu$_3$P)Pd; upper right: (*t*Bu-Amphos)Pd; lower left (*t*Bu-Pip-phos)Pd; lower right (Cy-Pip-phos)Pd (C = black, H = light grey, Pd = dark grey, P = horizontal lines, N = grid lines). These geometries were used to determine cone angles shown in Table 1.

Sterically Demanding Dialkylarylphosphanes

Buchwald has shown that 2-(dialkylphosphanyl)biphenyl ligands give active catalysts for a variety of coupling reactions of aryl bromides and chlorides under mild conditions.[6,42,43,76] Recently several hydrophilic analogs of these ligands have been reported to promote cross-coupling reactions of aryl chlorides in polar solvents (Figure 8). Plenio[69] reported the synthesis of **11**, which was applied to the Suzuki coupling of aryl chlorides in a DMSO/heptane solvent mixture. The catalyst derived from **11** gave higher initial TOFs than that derived from **9**, but was reported to be much less stable during recycling studies. No yields were reported for this ligand system, possibly due to the short lifetime of catalysts derived from **11**.

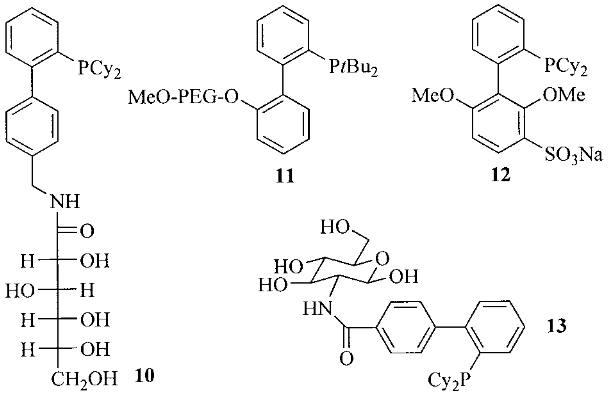
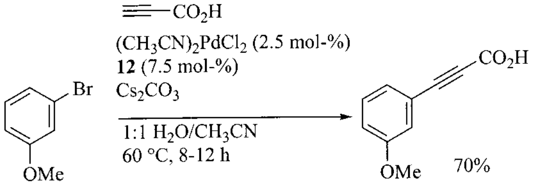


Figure 8. Hydrophilic 2-(dialkylphosphanyl)biphenyl ligands.

Ligand **10** was the first example of a hydrophilic 2-(phosphanyl)biphenyl ligand.[22] In combination with $Pd(OAc)_2$, this ligand gave excellent yields in the Suzuki coupling of a variety of activated aryl chlorides at 80 °C using only 0.1 mol-% Pd. The one example of a deactivated aryl chloride, 4-chloroanisole, required 2 mol% Pd to give a 79% yield. Sinou and Framery[77] reported a similar glucosamine-based ligand (**13**). The catalyst derived from **13** was only effective for highly activated aryl chlorides, such as 1-chloro-4-nitrobenzene. Despite its similarities to **10**, **13** gave a less effective catalyst for the Suzuki coupling of non-activated aryl chlorides. The recyclability of catalysts derived from **10** and **13** was not reported.

Buchwald[78] recently reported a sulfonated 2-(phosphanyl)biphenyl ligand (**12**) based on their highly effective S-Phos ligand.[76] Ligand **12** provides the first general catalyst for the Suzuki coupling of aryl chlorides in aqueous solvents under mild conditions. A wide variety of aryl chlorides could be arylated in excellent yields with reaction temperatures ranging from room temperature to 100 °C. Electron-rich and sterically hindered aryl chlorides were tolerated by this catalyst system. Ligand **12** was also successfully applied to the Sonogashira coupling of aryl bromides and chlorides. Significantly, **12**/Pd was the first catalyst system to couple a deactivated aryl bromide with propiolic acid [Equation (2)].



(2)

Palladacycles

Palladacycles have attracted much attention recently as precursors to active cross-coupling catalysts.[79,80] Bedford[81] and Buchwald[82] have reported the use of hydrophobic palladacycle/sterically demanding phosphane complexes for aqueous-phase Suzuki and Hartwig–Buchwald couplings in aqueous solvents, respectively. There are few examples of hydrophilic palladacycle precursors in the literature, however. Nájera[83] reported that the oxime-derived palladacycle **14** (Figure 9) was an effective precatalyst for the Suzuki coupling of aryl chlorides in refluxing water. Turnover numbers up to 7,700 mol/mol Pd were achieved with an activated aryl chloride, but electron-rich aryl chlorides gave modest yields in most cases. The oxime palladacycles have been attached to silica and used as heterogeneous catalysts in Suzuki couplings of activated aryl chlorides. The resulting heterogeneous catalyst (**15**) could be used for 8 reaction cycles in the coupling of 4-chloroacetophenone and phenylboronic acid at 100 °C without loss of activity.[84] No evidence of palladium leaching from the heterogeneous catalyst was observed in these studies.

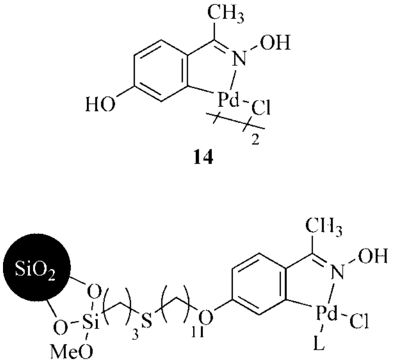


Figure 9. Hydrophilic oxime-derived palladacycles.

We have prepared several N–C palladacycles with hydrophilic substituents. None of these were effect precatalysts on their own, but **16** and **17** gave active catalysts for Suzuki couplings of aryl bromides in aqueous solvents at 80 °C when combined with tBu-Amphos (Figure 10), while catalysts derived from **18** and **19** were ineffective.[85] Complexes **16** and **17** act as precursors to the formation of the catalytically active $(t\text{Bu-Amphos})_2Pd^0$ species, although the identity of the N–C ligand does appear to affect the activity and lifetime of the resulting catalyst. The catalyst derived from **17** could be recycled eleven times in the coupling of 4-bromotoluene and phenylboronic acid at 80 °C in water before losing activity, while that derived from **16** began to lose ac-

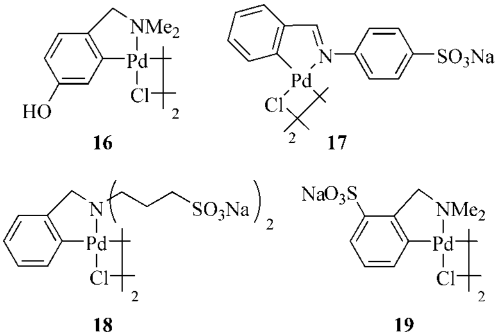


Figure 10. Hydrophilic palladacyclic catalyst precursors.

tivity after only four cycles (Figure 11). The catalyst derived from $Pd(OAc)_2$ became deactivated after only three cycles, which is similar to the result obtained with this catalyst system at room temperature.[72]

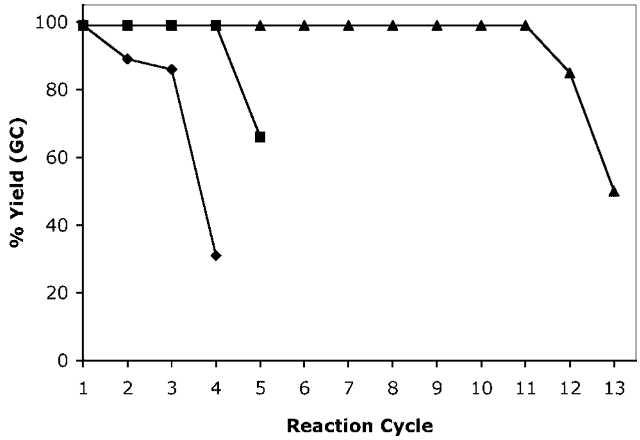


Figure 11. Recycling of *t*Bu-Amphos/Pd catalyst systems in the Suzuki coupling of 4-bromotoluene and phenylboronic acid (2 mol% Pd, 80 °C, 1 h/cycle). $Pd(OAc)_2$ (diamond), **16** (square), **17** (triangle).

N-Heterocyclic Carbene Ligands

Ligands based on the stable imidazol-2-ylidenes (N-heterocyclic carbenes, NHC) reported by Arduengo[86] have become widely used in palladium-catalyzed cross coupling.[87] Although there have been a few examples of hydrophilic NHC–metal complexes reported,[88–90] there are no examples of the use of hydrophilic NHCs as ligands for palladium-catalyzed coupling reactions. Catalysts derived from hydrophobic imidazolium salts and palladium have been applied to aqueous-phase cross-coupling reactions, however. Özdemir has reported that NHCs derived from imidazolinium (Figure 12, **20**),[91] benzimidazolium (**21**),[92,93] and tetrahydrodiazepinium (**22**)[94] salts gave effective catalysts for the Suzuki coupling of aryl chlorides in aqueous DMF at 80 °C. Each class of NHC precursor appeared to give similar activities, which may suggest that the active species is not a Pd–carbene complex, although studies to address this question have not been performed. Because the NHC ligands are hydrophobic, the resulting catalysts likely could not be recycled in an aqueous biphasic solvent system. A polystyrene-supported bis(imidazol-2-ylidene)palladium catalyst system (**23**) has been shown to be an effective and recyclable catalyst for the room temperature Suzuki coupling of aryl bromides in aqueous DMF.[95] The supported catalyst could be used 5 times for the Suzuki coupling of 4-bromotoluene at room temperature with no loss in catalyst efficiency.

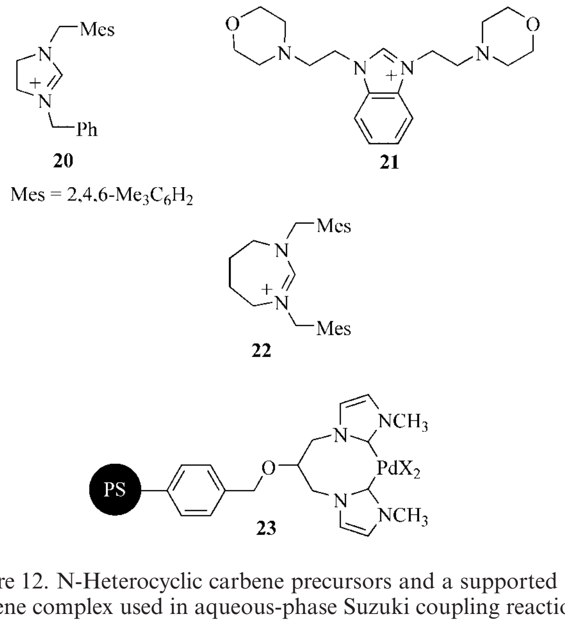


Figure 12. N-Heterocyclic carbene precursors and a supported Pd-carbene complex used in aqueous-phase Suzuki coupling reactions.

Conclusion

Significant progress has been made in the past several years towards the goal of developing hydrophobic catalyst systems capable of aqueous-phase cross-coupling reactions of aryl bromides and aryl chlorides at mild temperatures with high catalyst efficiencies. These advances have largely been achieved by moving beyond the triarylphosphane scaffold found in TPPTS. The current state-of-the-art systems are based on hydrophilic, sterically demanding trialkyl- or dialkylarylphosphanes. In contrast to phosphanes, hydrophilic NHC ligands that are effective for palladium-catalyzed cross-coupling reactions remain an unrealized goal, despite their successful use as ligands in organic solvents. While significant advances have been made in activating aryl bromides and chlorides under mild conditions for Suzuki and Sonogashira coupling reactions, there have been relatively few reports of efficient, hydrophilic catalyst systems for other synthetically important couplings, such as the Heck and Hartwig–Buchwald couplings. In general, the Suzuki coupling has been found to be relatively easy to accomplish, while the Heck and Hartwig–Buchwald couplings can be accomplished with a much smaller subset of ligands. Therefore, the lack of effective catalysts for aqueous-phase Heck and Hartwig–Buchwald reactions of aryl chlorides should represent an important target for future efforts in this field.

Acknowledgments

Funding for our work in this area by the National Science Foundation (CHE-0124255), the donors of the Petroleum Research Fund administered by the American Chemical Society, and the School of Mines and Energy Development at The University of Alabama is gratefully acknowledged. I am deeply indebted to the students and collaborators who have made our research in this area possible.

---

[1] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
[2] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168.
[3] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.

[4] T. N. Mitchell, in: *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH Verlag GmbH, Weinheim, Germany, **1998**, pp. 167–202.
[5] E.-i. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2017.
[6] J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818.
[7] J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067.
[8] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
[9] B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.
[10] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889–900.
[11] H.-U. Blaser, A. F. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *346*, 1583–1598.
[12] C.-J. Li, *Organic Reactions in Organic Media*; Wiley, New York, **1997**, p. 199.
[13] C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165.
[14] D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521–527.
[15] R. A. Sheldon, *CHEMTECH* **1994**, *24*, 38–47.
[16] C. Jiménez-González, A. D. Curzons, D. J. C. Constable, V. L. Cunningham, *Int. J. LCA* **2004**, *9*, 114–121.
[17] A. L. Casalnuovo, J. C. Calabrese, *J. Am. Chem. Soc.* **1990**, *112*, 4324–4330.
[18] A. Hessler, O. Stelzer, H. Dibowski, K. Worm, F. P. Schmidtchen, *J. Org. Chem.* **1997**, *62*, 2362–2369.
[19] M. Beller, J. G. E. Krauter, A. Zapf, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 772–774.
[20] B. A. Harper, D. A. Knight, C. George, S. L. Brandow, W. J. Dressick, C. S. Dalcey, T. L. Schull, *Inorg. Chem.* **2003**, *42*, 516–524.
[21] E. Genin, R. Amengual, V. Michelet, M. Savignac, A. Jutand, L. Neuville, J. P. Genêt, *Adv. Synth. Catal.* **2004**, *346*, 1733–1741.
[22] M. Nishimura, M. Ueda, N. Miyaura, *Tetrahedron* **2002**, *58*, 5779–5787.
[23] S. Parisot, R. Kolodziuk, C. Goux-Henry, A. Iourtchenko, D. Sinou, *Tetrahedron Lett.* **2002**, *43*, 7397–7400.
[24] F. Joó, Á. Kathó, *J. Mol. Cat A. Chem.* **1997**, *116*, 3–26.
[25] J. P. Genêt, M. Savignac, *J. Organomet. Chem.* **1999**, *576*, 305–317.
[26] I. P. Beletskaya, A. V. Cheprakov, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), John Wiley & Sons, New York, **2002**, vol. 2, pp. 2957–3006.
[27] K. H. Shaughnessy, R. B. DeVasher, *Curr. Org. Chem.* **2005**, *9*, 585–604.
[28] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771–11835.
[29] N. E. Leadbeater, *Chem. Commun.* **2005**, 2881–2902.
[30] A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
[31] H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
[32] A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704–8705.
[33] X. Fu, S. Zhang, J. Yin, T. L. McAllister, S. A. Jiang, C.-H. Tann, T. K. Thiruvengadam, F. Zhang, *Tetrahedron Lett.* **2002**, *43*, 573–576.
[34] A. Zapf, *Angew. Chem. Int. Ed.* **2003**, *42*, 5394–5399.
[35] M. Beller, A. C. Frisch, *Angew. Chem. Int. Ed.* **2005**, *44*, 674–688.
[36] P. Fitton, E. A. Rick, *J. Organomet. Chem.* **1971**, *28*, 287–291.
[37] J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580.
[38] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
[39] A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
[40] A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155.
[41] A. Ehrentraut, A. Zapf, M. Beller, *J. Mol. Cat. A: Chem.* **2002**, *182–183*, 515–523.
[42] J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158–1174.
[43] J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.
[44] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876.
[45] F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Reiermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983–2990.
[46] S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett.* **2000**, *2*, 1423–1426.
[47] M. S. Viciu, O. Navarro, R. F. Germaneau, R. A. Kelly III, W. Sommer, N. Marion, E. D. Stevens, L. Cavallo, S. P. Nolan, *Organometallics* **2004**, *23*, 1629–1635.
[48] R. Singh, M. S. Viciu, N. Kramareva, O. Navarro, S. P. Nolan, *Org. Lett.* **2005**, *7*, 1829–1832.
[49] F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 6944–6945.
[50] A. Arcadi, G. Cerichelli, M. Chiarini, M. Correa, D. Zorzan, *Eur. J. Org. Chem.* **2003**, 4080–4086.
[51] L. Liu, Y. Zhang, Y. Wang, *J. Org. Chem.* **2005**, *70*, 6122–6125.
[52] R. K. Arvela, N. E. Leadbeater, *Org. Lett.* **2005**, *7*, 2101–2104.
[53] J.-C. Galland, M. Savignac, J.-P. Genêt, *Tetrahedron Lett.* **1999**, *40*, 2323–2326.
[54] H. Gulyás, Á. Szöllösy, B. E. Hanson, J. Bakos, *Tetrahedron Lett.* **2002**, *43*, 2543–2546.
[55] H. Gulyás, Á. Szöllösy, P. Szabó, P. Halmos, J. Bakos, *Eur. J. Org. Chem.* **2003**, 2775–2781.
[56] L. R. Moore, K. H. Shaughnessy, *Org. Lett.* **2004**, *6*, 225–228.
[57] H. Gulyás, A. C. Bényei, J. Bakos, *Inorg. Chim. Acta* **2004**, *357*, 3094–3098.
[58] B. C. Taverner, *J. Comput. Chem.* **1996**, *17*, 1612–1623.
[59] L. R. Moore, E. C. Western, J. M. Spruell, R. Craciun, D. A. Dixon, K. H. Shaughnessy, **2005**, unpublished results.
[60] E. C. Western, J. R. Daft, E. M. Johnson II, P. M. Gannett, K. H. Shaughnessy, *J. Org. Chem.* **2003**, *68*, 6767–6774.
[61] E. C. Western, K. H. Shaughnessy, *J. Org. Chem.* **2005**, *70*, 6378–6388.
[62] G. Y. Li, *J. Org. Chem.* **2002**, *67*, 3643–3650.
[63] G. Y. Li, G. Zeng, A. F. Noonan, *J. Org. Chem.* **2001**, *66*, 8677–8681.
[64] C. Wolf, R. Lerebours, *J. Org. Chem.* **2003**, *68*, 7551–7554.
[65] C. Wolf, R. Lerebours, *Org. Biomol. Chem.* **2004**, *2*, 2161–2164.
[66] C. Wolf, R. Lerebours, *Org. Lett.* **2004**, *6*, 1147–1150.
[67] R. Lerebours, C. Wolf, *Synthesis* **2005**, 2287–2292.
[68] A. Köllhofer, H. Plenio, *Chem. Eur. J.* **2003**, *6*, 1416–1425.
[69] M. an der Heiden, H. Plenio, *Chem. Eur. J.* **2004**, *10*, 1789–1797.
[70] B. Mohr, D. M. Lynn, R. H. Grubbs, *Organometallics* **1996**, *15*, 4317–4325.
[71] K. H. Shaughnessy, R. S. Booth, *Org. Lett.* **2001**, *3*, 2757–2759.
[72] R. B. DeVasher, L. R. Moore, K. H. Shaughnessy, *J. Org. Chem.* **2004**, *69*, 7919–7927.
[73] R. B. DeVasher, J. M. Spruell, D. A. Dixon, G. A. Broker, S. T. Griffin, R. D. Rogers, K. H. Shaughnessy, *Organometallics* **2005**, *24*, 962–971.
[74] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.
[75] C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2953–2956.
[76] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
[77] A. Konovets, A. Penciu, E. Framery, N. Percina, C. Goux-Henry, D. Sinou, *Tetrahedron Lett.* **2005**, *46*, 3205–3208.
[78] K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2005**, *44*, 6175–6177.
[79] I. P. Beletskaya, A. V. Cheprakov, *J. Organomet. Chem.* **2004**, *689*, 4055–4082.

[80] J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571.

[81] R. B. Bedford, M. E. Blake, C. P. Butts, D. Holder, *Chem. Commun.* **2003**, 466–467.

[82] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

[83] L. Botella, C. Nájera, *J. Organomet. Chem.* **2002**, *663*, 46–57.

[84] C. Baleizão, A. Corma, H. García, A. Leyva, *J. Org. Chem.* **2004**, *69*, 439–446.

[85] R. Huang, K. H. Shaughnessy, **2005**, unpublished results.

[86] A. J. Arduengo III, *Acc. Chem. Res.* **1999**, *32*, 913–921.

[87] N. M. Scott, S. P. Nolan, *Eur. J. Inorg. Chem.* **2005**, 1815–1828.

[88] I. Özdemir, B. Yigit, B. Çetinkaya, D. Ülkü, M. N. Tahir, C. Arici, *J. Organomet. Chem.* **2001**, *633*, 27–32.

[89] A. Melaiye, R. S. Simons, A. Milsted, F. Pingitore, C. Wesdemiotis, C. A. Tessier, W. J. Youngs, *J. Med. Chem.* **2004**, *47*, 973–977.

[90] J. P. Gallivan, J. P. Jordan, R. H. Grubbs, *Tetrahedron Lett.* **2005**, *46*, 2577–2580.

[91] I. Özdemir, S. Demir, S. Yasar, B. Çetinkaya, *Appl. Organomet. Chem.* **2005**, *19*, 55–58.

[92] I. Özdemir, Y. Gök, N. Gürbüz, E. Çetinkaya, B. Çetinkaya, *Heteroat. Chem.* **2004**, *15*, 419–423.

[93] I. Özdemir, Y. Gök, N. Gürbüz, E. Çetinkaya, B. Çetinkaya, *Synth. Commun.* **2004**, *34*, 4135–4144.

[94] I. Özdemir, N. Gürbüz, Y. Gök, E. Çetinkaya, B. Çetinkaya, *Synlett* **2005**, 2394–2396.

[95] T. Kang, Q. Feng, M. Luo, *Synlett* **2005**, 2305–2308.

Received: December 12, 2005