Forum

Mizoroki–Heck Coupling Using Immobilized Molecular Precatalysts: Leaching Active Species from Pd Pincers, Entrapped Pd Salts, and Pd NHC Complexes

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The Mizoroki–Heck reaction is a palladium-catalyzed reaction of both practical importance and scientific significance. Two challenges currently faced by practitioners of the Heck and other palladium-catalyzed coupling reactions are (i) minimizing the costs associated with this reaction by developing high TON catalysts or facilitating catalyst recovery and (ii) elucidating the nature of the active species when using various different precatalysts. These two challenges, one practical and one fundamental, served as our motivation in our studies of immobilized molecular palladium(II) complexes as precatalysts in Mizoroki–Heck reactions. This Forum Article describes our investigations in this area, highlighting our approach to the elucidation of the active catalyst by combining kinetic and poisoning studies of several different related precatalysts, our development of new, selective catalyst poisons, and our quest for stable, recyclable supported Heck, Suzuki, and Sonogashira coupling catalysts. Under high-temperature conditions (120 °C), all precatalysts studied are conclusively shown to decompose, liberating soluble, active palladium(0) species that are the true catalysts. Techniques for the elucidation of the nature of the truly active Pd species are enumerated.

Introduction

The Mizoroki—Heck reaction,[1–5] the coupling of aryl halides with terminal olefins, is among the most important palladium-catalyzed transformations in organic synthesis. It is both a critical methodology for creating C—C bonds on either the laboratory or industrial scale[6–8] and a favorite test reaction for new palladium precatalysts.[9] From a catalysis science perspective, the reaction is of extreme interest because virtually every form of palladium can promote some Heck reactions under some conditions.[10] From supported palladium (Pd/C, Pd/SiO$_2$, and Pd/NaY), to soluble or polymer-entrapped palladium nanoparticles, to metal—ligand complexes (preassembled or in situ produced), to simple palladium salts like Pd(OAc)$_2$, nearly every common (and not so common) form of palladium has been successfully demonstrated as a precatalyst in Heck catalysis. Because the nature of the catalytically active species is not the central theme of many studies that utilize the palladium-catalyzed Heck reaction in organic synthesis, it is often assumed that the form of palladium added to the reactor or flask is the form that promotes the catalysis. However, studies over the past 10—15 years have increasingly focused on two topics. The first is the generation of a molecular-level understanding of palladium-mediated Heck catalysis, and it is clear now that, more often than not, the added palladium significantly restructures under reaction conditions to generate an active species that is quite different from the form added to the reactor.[10,11] Indeed, a comprehensive understanding of the mechanisms of high-temperature[12] Heck catalysis has been

(1) Heck, R. F. *Pure Appl. Chem.* **1978**, *50*, 691.
(2) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
(3) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.
(4) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
(5) Mori, K.; Mizoroki, T.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505.
(6) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.
(7) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101.
(8) Blaser, H. U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583.
(9) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(10) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.
(11) de Vries, J. *Dalton Trans.* **2006**, 421.
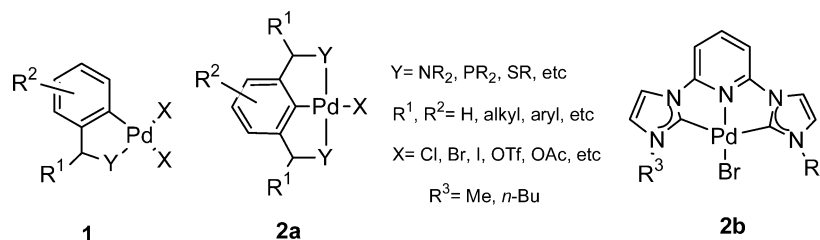
Figure 1. Examples of half-pincer (**1**) and pincer (**2**) palladacycles (Reprinted with permission from reference 71. Copyright Elsevier 2004.)

assembled over the past decade, starting with the work of Schmidt[13-20] and including key contributions from Arai,[21-23] Köhler,[24-27] Biffis,[28-30] de Vries,[11,31,32] and others.[10] The second modern thrust has been the development of effective donor ligands for low-temperature[12] C−C bond coupling reactions using the low cost but difficult to activate family of aryl chlorides. This topic will not be covered in this Forum Article, and the reader is referred to the recent reviews by Bedford[33] and Fu.[34]

Several years ago, we began our initial investigations into palladium-catalyzed Heck transformations. Our interests centered on Heck reactions catalyzed by supported forms of coordination complexes of palladium for both practical and scientific reasons. In the commercial application of palladium catalysts for Heck coupling, palladium recovery is important for meeting product purity specifications in the pharmaceutical field as well as for minimizing catalyst costs.[28,35,36] Immobilization of soluble homogeneous catalysts has been a topic of interest for many years for this reason. Scientifically, the field was in the midst of a debate on the nature of the active species generated using the myriad of different precatalysts reported to date. In addition, both the nature of the active species and the mechanism of the Heck coupling were unclear when using palladacycle-based precatalysts. Palladacycles, including both pincers[37-45] and half-pincers,[46-48] as we chose to refer to them, had been developed since 1995 as novel, highly effective precatalysts for Heck coupling reactions (Figure 1). These palladium(II) complexes were shown to be stable in the presence of various solvents at high temperatures, and fractions of the palladacycle (sometimes nearly all of the complex) added to a reaction could be recovered intact after the reaction was completed.[37,43,44] Furthermore, palladium black, a common residue left over after Heck reactions using other common precatalysts, was often not observed after reactions using palladacycles as precatalysts. These observations implied that a classical Pd-(0)−Pd(II) Heck cycle[49] might not be in operation. Observations such as these led to an early hypothesis that palladacycle complexes operated by a different mechanism, and a Pd-(II)−Pd(IV) cycle was proposed.[46-48] In 1998, the idea gained a more solid footing with a publication that described the hypothesized cycle in some detail.[10,50,51] The hypothetical Pd(II)−Pd(IV) mechanism then became a topic of investigation by several authors, who sought to uncover definitive data that would support or refute this catalytic cycle.[10] Simultaneously, many researchers using palladacycles in Heck reactions began to invoke the possible operation of this mechanism in their publications.

A series of investigations by different authors began to cast serious doubt on the operation of a Pd(II)−Pd(IV) cycle when using half-pincer palladacycles as precatalysts. Early

(12) A critical overview[10] of the available data on Heck and Suzuki coupling reactions suggests that at high temperatures (e.g., >~120 °C in the Heck reaction) nearly all precatalysts decompose to liberate soluble "ligand-free" molecular species that are the true active catalysts during couplings of iodo or bromo halides. In contrast, at lower temperatures (e.g., <~80 °C in the Heck reaction), preassembled or in situ produced molecular metal−ligand complexes may function as active species. Under these conditions, specific donor ligands can significantly impact the catalysis. See de Vries' original discussion[11] of the temperature regimes in Heck catalysis for further details.
(13) Schmidt, A. F.; Smirnov, V. V. *J. Mol. Catal. A* **2003**, *203*, 75.
(14) Schmidt, A. F.; Smirnov, V. V. *Kinet. Catal.* **2003**, *44*, 518.
(15) Schmidt, A. F.; Khalaika, A. *Kinet. Catal.* **1998**, *39*, 803.
(16) Schmidt, A. F.; Khalaika, A.; Bylkova, V. G. *Kinet. Catal.* **1998**, *39*, 194.
(17) Schmidt, A. F.; Khalaika, A.; Li, D. H. *Kinet. Catal.* **1998**, *39*, 299.
(18) Schmidt, A. F.; Khalaika, A.; Nindakova, L. O.; Shmidt, E. Y. *Kinet. Catal.* **1998**, *39*, 200.
(19) Schmidt, A. F.; Mametova, L. V. *Kinet. Catal.* **1996**, *37*, 406.
(20) Schmidt, A. F.; Al-Halaiqa, A.; Smirnov, V. V. *J. Mol. Catal. A* **2006**, *250*, 131.
(21) Zhao, F. Y.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem.—Eur. J.* **2000**, *6*, 843.
(22) Zhao, F. Y.; Murakami, K.; Shirai, M.; Arai, M. *J. Catal.* **2000**, *194*, 479.
(23) Zhao, F. Y.; Shirai, M.; Arai, M. *J. Mol. Catal. A* **2000**, *154*, 39.
(24) Heidenreich, R. G.; Kohler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118.
(25) Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J.; Köhler, K. *J. Mol. Catal. A* **2002**, *182*, 499.
(26) Wagner, M.; Kohler, K.; Djakovitch, L.; Weinkauf, S.; Hagen, V.; Muhler, M. *Top. Catal.* **2000**, *13*, 319.
(27) Prockl, S. S.; Kleist, W.; Gruber, M. A.; Köhler, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881.
(28) Biffis, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A* **2001**, *173*, 249.
(29) Biffis, A.; Zecca, M.; Basato, M. *Eur. J. Inorg. Chem.* **2001**, 1131.
(30) Biffis, A. *J. Mol. Catal. A* **2001**, *165*, 303.
(31) de Vries, A.; Parlevliet, F.; Schmieder-van de Vondervoort, L.; Mommers, J.; Henderickx, H.; Walet, M.; de Vries, J. *Adv. Synth. Catal.* **2002**, *344*, 996.
(32) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.
(33) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283.
(34) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
(35) Bhanage, B. M.; Arai, M. *Catal. Rev., Sci. Eng.* **2001**, *43*, 315.
(36) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
(37) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287.
(38) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379.
(39) Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redon, R.; Cramer, R. E.; Jensen, C. M. *Inorg. Chim. Acta* **2000**, *300*, 958.
(40) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619.
(41) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357.
(42) Ohff, M.; Ohff, A.; Van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1998**, *120*, 3273.
(43) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y. S. *J. Am. Chem. Soc.* **1999**, *121*, 9531.
(44) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058.
(45) Takenaka, K.; Minakawa, M.; Uozomi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 12273.

kinetic studies by Beller suggested that the palladium(II) precatalyst was reduced in situ to form a palladium(0) species that was truly active.[52] Work with immobilized forms of half-pincer palladacycles by Nowotny[53] and Bedford[54] in Heck and Suzuki couplings showed leaching of active species from the support, with the leached species identified as palladium-(0) species. Beletskaya[55] used kinetic studies and Gladysz[56,57] careful investigations of fluorous-tagged half-pincer complexes to conclude that the catalysis occurred via a classic Pd(0)−Pd(II) cycle. de Vries and co-workers showed that a prototypical half-pincer palladacycle and the simple salt Pd-(OAc)₂ behaved kinetically the same in Heck couplings and concluded that they created the same type of active species.[32] Most recently, Dupont has presented a detailed description of the activation of half-pincer palladacycles, ultimately yielding active molecular palladium(0) species.[58] These studies strongly suggest that most or all of the catalysis occurs via a classic Pd(0)−Pd(II) cycle, although no studies provided enough data to conclusively rule out some smaller fraction of the catalysis occurring by a Pd(II)−Pd(IV) cycle mediated by an intact palladacycle complex. A detailed account of the development of this field can be found in several reviews.[59−62]

While the investigations above described the activation process of the half-pincer palladacycle family of precatalysts in Heck coupling chemistry, the full pincer palladacycles developed from 1997 onward were less frequently studied, and their activation for Heck coupling remained unclear in 2003 when we began our investigations. Indeed, for these precatalysts, the published papers at that time exclusively suggested that a Pd(II)−Pd(IV) cycle likely operated.[37−40,42,63−65] Whereas the half-pincer palladacycles needed to break a

strong Pd−C bond and an additional Pd−L bond (where most often L = N, P, and S) to generate the active, ligand-free palladium(0) moiety suggested to be the active species, full pincer complexes must break an additional Pd−L bond. The tridentate nature of the pincer ligand was thus suggested to contribute additional stability to the complex, and its decomposition under reaction conditions was deemed unlikely. For example, Bergbreiter published a number of investigations describing the use of soluble polymer-supported Pd(II)−SCS pincer complexes in Heck couplings.[43,44,66−68] After use in a single reaction, the polymers could be recovered and effectively reused in subsequent reactions. In addition, after use in a reaction, the palladium-containing polymer appeared to be similar to the one before the reaction using various analytical techniques. Alper also reported "recyclable" silica-supported Pd(II)−PCP complex catalysts for Heck coupling.[69] These data suggested that a stable catalyst was in hand. In 2001, Beletskaya hypothesized that all palladacycles were precatalysts that decompose to form palladium(0) active species, except possibly the "truly robust" PCP pincer palladacycles that they reported later as Heck catalysts.[70] Given these data, we identified palladium pincers as perhaps the most promising complexes for use as stable, immobilized Heck coupling catalysts and began our development of polymer- and silica-supported Pd(II)−SCS and −PCP complexes for Heck coupling. Our goals were (i) the development of stable and recyclable immobilized palladium-(II) pincer complexes and (ii) the elucidation of their reactivity on the molecular level.

## Establishing the Reactivity of Pd−SCS and −PCP Pincer Complexes in Heck Catalysis

Comparing Small-Molecule, Soluble Polymer-Supported and Insoluble Silica-Supported SCS Pincer Complexes. In 2003, we embarked on a collaboration between our two groups that involved palladium-mediated Heck coupling catalysis. Pd(II)−SCS pincer complexes were targeted for immobilization on both insoluble mesoporous silica and polymer resin supports and soluble poly(norbornene) supports. Building off the pioneering work of Bergbreiter and co-workers in this area,[43,44] we selected Pd-(II)−SCS pincers with an ether linkage to the support (SCS−O ligands; Figure 2)[71] and Pd(II)−SCS pincers with an amide or urea linkage to the support (SCS−N ligands; Figure 3).[72] Our first investigations involved Pd(II)−SCS−O pincer complexes because synthetic pathways had already been developed for immobilization of these complexes onto poly(norbornene) by the Weck group.[73]

(46) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848.
(47) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
(48) Herrmann, W. A.; Reisinger, C. P.; Ofele, K.; Brossmer, C.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1996**, *108*, 51.
(49) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
(50) A paper claiming isolation of a palladium(IV) intermediate that could be implicated in a Pd(II)−Pd(IV) cycle has since been withdrawn. Brunel, J. M.; Hirlemann, M. H.; Heumann, A.; Buono, G. *Chem. Commun.* **2000**, 1869.
(51) Shaw, B. L. *New J. Chem.* **1998**, *22*, 77.
(52) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29.
(53) Nowotny, M.; Hanefeld, U.; van Koningsveld, H.; Maschmeyer, T. *Chem. Commun.* **2000**, 1877.
(54) Bedford, R. B.; Cazin, C. S. J.; Hursthouse, M. B.; Light, M. E.; Pike, K. J.; Wimperis, S. *J. Organomet. Chem.* **2001**, *633*, 173.
(55) Beletskaya, I. P.; Kashin, A. N.; Karlstedt, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89.
(56) Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, *4*, 1993.
(57) Rocaboy, C.; Gladysz, J. A. *New J. Chem.* **2003**, *27*, 39.
(58) Consorti, C. S.; Flores, F. R.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 12054.
(59) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055.
(60) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.
(61) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917.
(62) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.
(63) Ohff, M.; Ohff, A.; vanderBoom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.
(64) Sjövall, S.; Wendt, O. F.; Andersson, C. *J. Chem. Soc., Dalton Trans.* **2002**, 1396.
(65) Hossain, M. A.; Lucarini, S.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2004**, *43*, 7275.
(66) Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004**, *6*, 280.
(67) Bergbreiter, D. E.; Li, J. *Chem. Commun.* **2004**, 42.
(68) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 11105.
(69) Chanthateyanonth, R.; Alper, H. *J. Mol. Catal. A* **2003**, *201*, 23.
(70) Beletskaya, I. P.; Chuchuryukin, A. V.; van Koten, G.; Dijkstra, H. P.; van Klink, G. P. M.; Kashin, A. N.; Nefedov, S. E.; Eremenko, I. L. *Russ. J. Inorg. Chem.* **2003**, *39*, 1268.
(71) Yu, K. Q.; Sommer, W.; Weck, M.; Jones, C. W. *J. Catal.* **2004**, *226*, 101.
(72) Yu, K. Q.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161.
(73) Pollino, J. M.; Weck, M. *Org. Lett.* **2002**, *4*, 753.
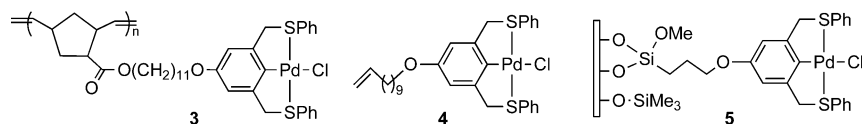
Figure 2. Pd(II)−SCS−O pincer complexes used in our studies. Soluble precatalysts included a poly(norbornene)-supported complex, **3**, and a small-molecule complex, **4**. A mesoporous silica-supported insoluble precatalyst, **5**, was also utilized.
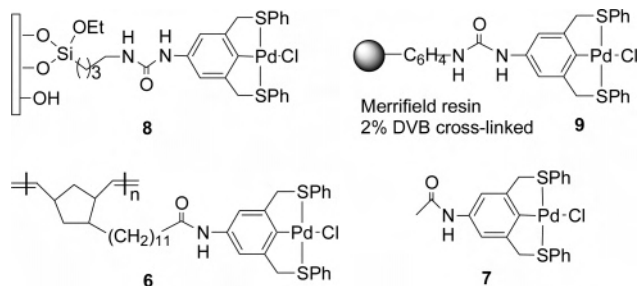
Figure 3. Pd(II)−SCS−N pincer complexes used in our studies. Soluble precatalysts included a poly(norbornene) supported complex, **6**, and a small-molecule complex, **7**. A mesoporous silica-supported insoluble precatalyst, **8**, and a Merrifield resin-supported complex, **9**, were also utilized.
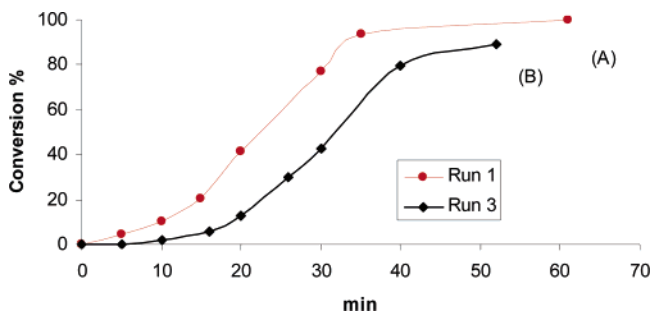
Figure 4. Conversion of iodobenzene in the Heck coupling with *n*-butyl acrylate at 120 °C in DMF using triethylamine as the base and **5** as the precatalyst. The first use of the precatalyst is shown in curve A and the third use in curve B (Reprinted with permission from reference 71. Copyright 2004 Elsevier.)

Knowing the history of the half-palladacycle systems and their decomposition into ligand-free palladium(0) species that were hypothesized to be active, we first began our catalytic investigation of the SCS−O complexes[71] with kinetic studies aimed at elucidating whether we had a catalyst or a precatalyst in hand. Our early kinetic studies of the coupling of iodobenzene and *n*-butyl acrylate in *N,N*-dimethylformamide (DMF) with triethylamine as the base clearly showed the presence of an s-shaped curve, a sign of an induction period in the catalysis (Figure 4). There also was a marked change in the reaction rate upon recycling. Such kinetics were apparent with all of the SCS−O catalysts studied, including the homogeneous, small-molecule complex **4**, the silica-supported complex **5**, and the poly(norbornene)-supported complex **3**. Whereas Bergbreiter only studied soluble precatalysts, our study that included insoluble silica-supported precatalysts allowed us to carry out simple tests for the presence of leached species: filtration or split tests.[74] By removing the silica-supported complex midway through a reaction and allowing the solid-free filtrate to continue to react under inert conditions, we showed that the catalysis continued, a sure sign of leaching of active palladium species

from the solid support. Such a split test would be difficult or impossible to do with only a soluble polymer-supported complex (as in Bergbreiter's case) because complete removal of residual oligomer-supported palladium would be difficult to rule out using precipitation as the method for polymer removal. A three-phase test,[75−79] whereby one reagent was immobilized on a separate solid phase, was also used to effectively demonstrate the presence of soluble active catalytic species.[71] Loss of palladium was verified by elemental analysis of the solid catalyst before and after use.

Insoluble Polymeric Poisons as Crucial Tools in Characterizing Catalysis by Supported vs Leached Species. The above data clearly supported catalysis by leached species, but we did not know if there was some fraction of catalysis associated with immobilized pincer complexes nor did we know the nature of the active species in solution. A poison that was selective for only soluble species was needed to discern whether any catalysis was associated with immobilized species.

Recalling the use of bulky or polymeric amines as basic poisons for accessible acid sites when using crystalline, porous solid catalysts (soluble sites or insoluble sites on the external surface of solids),[80,81] we surmised that such materials might work equally well for removing free palladium species from solution in coupling reactions. Indeed, it was found that the literature described that the addition of a large excess of copolymers of poly(vinylpyridine) (PVPy) effectively extinguished the activity associated with palladium nanoparticle precatalysts in the Heck reactions,[82] while the addition of molecular pyridine merely slowed the reaction rate. Thus, the poisoning effect of PVPy was ascribed to its ability to coordinate to the palladium and pull soluble, active species out of the solution by binding them tightly in a multidentate manner. We chose to use commercially available, lightly cross-linked PVPy resins that were insoluble under reaction conditions and too large to enter the pores of the mesoporous silica, SBA-15,[83] used to support our Pd−SCS−O complexes, as a poison for soluble palladium species. Inclusion of PVPy in the reaction media at the outset effectively suppressed the Heck catalysis.[71] The addition of PVPy after a fraction of the reagents had been

(74) Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485.

(75) Rebek, J. *Tetrahedron* **1979**, *35*, 723.
(76) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454.
(77) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112.
(78) Collman, J. P.; Kosydar, K. M.; Bressan, M.; Lamanna, W.; Garrett, T. *J. Am. Chem. Soc.* **1984**, *106*, 2569.
(79) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139.
(80) Jones, C. W.; Tsuji, K.; Davis, M. E. *Nature* **1998**, *393*, 52.
(81) Jones, C. W.; Davis, M. E. **1998**, unpublished work.
(82) Klingelhofer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Forster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116.
(83) Zhao, D. Y.; Feng, J. L.; Huo, Q. S.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*, 548.

Scheme 1. Coordination between Poly(norbornene)-SCS−O−PdCl, **3**, and Pyridine[a] (Reprinted with permission from reference 72. Copyright Wiley 2005.)
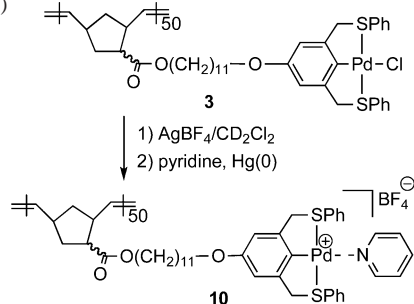
[a] Coordination was confirmed by ^{1}H NMR.

converted also effectively shut down the catalysis. These data conclusively showed that all activity was associated with soluble, leached species and there was no activity associated with immobilized sites.

While the above data definitively demonstrated that the leaching of palladium from the support was associated with the generation of active species, the nature of the actual leached species was unclear. Ligand-free palladium(0) could have been expelled from the immobilized site if the Pd−C and Pd−S bonds were broken. Alternatively, the entire pincer complex could have been leached via rupture of the Si−C or Si−O bonds tethering the complex to the silica surface. To probe this issue, we next utilized a mercury test to probe for the presence of active palladium(0) species.[71] The addition of mercury(0) to metal complex catalyzed reactions has been used for many years to test for catalysis by free metal(0) species.[84,85] It has been suggested that mercury(0) can amalgamate free metallic species, making them unavailable for catalysis. In contrast, metal−ligand complexes, especially those with the metal in elevated formal oxidation states, should be unaffected by the presence of mercury(0). To evaluate this hypothesis, we carried out a stoichiometric transformation where the palladium pincer remained a palladium(II) species—an exchange of the Pd−Cl group for a Pd−Py interaction—in the presence of excess mercury(0) (Scheme 1). Analysis of the reaction via ^{1}H NMR showed that the reaction occurred in the presence of mercury.[72,73] This suggested, as was previously established in the literature, that mercury(0) should not affect transformations with metal−ligand complexes such as palladium(II) pincers in elevated formal oxidation states. Thus, if an intact pincer were leached and if this catalyzed the Heck reaction by a Pd(II)−Pd(IV) cycle, it should be unaffected by mercury-(0). However, all of our catalysts were rendered completely inactive by treatment with mercury(0), a strong indication that all catalysis occurs via a Pd(0)−Pd(II) cycle.[71] These new data coupled with the experiments described above indicated that the only species active when using the Pd-(II)−SCS−O pincer species were palladium(0) moieties leached from the pincer ligand, and this precatalyst utilized the classical Heck catalytic cycle.

Bergbreiter indicated in his early publications that Pd(II)−SCS−O complexes appeared less stable than Pd(II)−SCS−N complexes.[43] Whereas traces of palladium black were evident after Heck catalysis using the ether-linked complexes, catalysis using polymer-tethered, amide-linked complexes showed no signs of decomposition.[43] To this end, we prepared a series of Pd(II)−SCS−N complexes with amide and urea linkages to mesoporous silica, poly(norbornene), and polymer resin supports and evaluated these new precatalysts, alongside small-molecule analogues (Figure 3), in the Heck coupling of iodobenzene and *n*-butyl acrylate at 120 °C.[72] Using the same probes as described above, we systematically demonstrated that these precatalysts also decompose to liberate soluble palladium(0) species that are the true active species in these Heck coupling reactions. Again, in this case, we could conclusively show that no catalysis occurred via the hypothetical Pd(II)−Pd(IV) cycle. Correspondence with Bergbreiter indicated that he had recently accumulated data independently that also supported these conclusions, and, together, our publications effectively closed the door on Heck catalysis via the Pd(II)−Pd(IV) cycle using Pd(II)−SCS precatalysts.[72,86] Nonetheless, publications suggesting such a cycle continue to appear.[65,87]

Reactivity of PCP Pincer Complexes in Heck Catalysis. At about the same time that we communicated our initial studies on Pd(II)−SCS complexes, Eberhard[88] reported an investigation into Pd(II)−PCP complexes in Heck catalysis. A detailed study of four phosphine- and phosphinite-palladium(II) complexes using kinetic and poisoning studies revealed that these complexes also decomposed to liberate palladium(0) species during high-temperature Heck coupling. However, the author could not rule out the possibility of some catalysis occurring via a Pd(II)−Pd(IV) cycle.

Pincer complexes based on PCP chelation of palladium were an obvious next step in our studies because the P−Pd bonds could impart the complex with increased stability compared to other pincer complexes. In addition, the presence of phosphorus in key positions in the ligand gave an additional NMR handle that we decided to use in efforts to elucidate the mechanism of decomposition. Our efforts to more fully characterize the palladium(II) pincer system further aided electronic structure characterization in C. David Sherrill's group and in situ and ex situ X-ray absorption spectroscopy characterization in Robert J. Davis' group.[89]

Our standard kinetic and poisoning studies outlined above were used to verify that all of the polymer- and silica-supported Pd(II)−PCP complexes also decomposed to liberate exclusively soluble, unsupported active species. The nature of the species linking the ligand to the support (PCP−O, ether vs PCP−N, amide; Figure 5; complexes **11**−**14**) had no major influence on the stability of the complex, with

(84) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855.
(85) Foley, P.; Dicosimo, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6713.

(86) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *Adv. Synth. Catal.* **2005**, *347*, 172.
(87) Yoon, M. S.; Ryu, D.; Kim, J.; Ahn, K. H. *Organometallics* **2006**, *25*, 2409.
(88) Eberhard, M. R. *Org. Lett.* **2004**, *6*, 2125.
(89) Sommer, W. J.; Yu, K. Q.; Sears, J. S.; Ji, Y. Y.; Zheng, X. L.; Davis, R. J.; Sherrill, C. D.; Jones, C. W.; Weck, M. *Organometallics* **2005**, *24*, 4351.
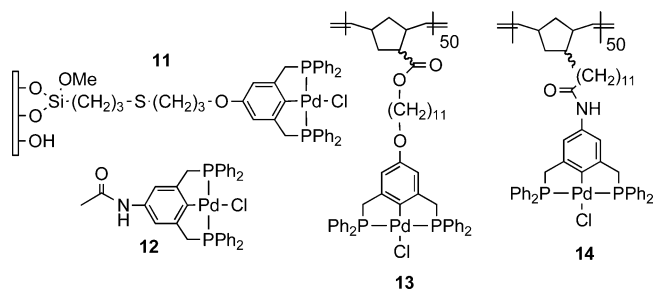
Figure 5. PCP complexes used in our studies of the Heck coupling of *n*-butyl acrylate and iodobenzene, including the insoluble silica-supported complex **11**, soluble small-molecule **12**, and poly(norbornene)-supported complexes **13** and **14** (Reprinted from reference 89.)

all catalysts liberating some active palladium(0) species under reaction conditions.[89]

On the basis of literature precedents for arm-off mechanisms whereby one of the L groups dechelates the palladium atom in the presence of other ligands, we suggested that this could be a plausible first step in the decomposition process under reaction conditions in the presence of organic nitrogen bases[45,90−92] (Scheme 2). Such a first step effectively creates a half-pincer complex with an additional amine base as a ligand. Hartwig and Louie have shown that half-pincer complexes like these can undergo a β-hydrogen elimination process to yield a palladium hydride and an iminium ion[93] (Scheme 2). The ligand can then be expelled from the palladium atom by hydride migration to the aromatic carbon bonded to the palladium, eliminating the Pd−C bond. To verify the possibility of this process, we characterized the stability of the small-molecule Pd(II)−PCP complex in the presence of triethylamine and iodobenzene in DMF via in situ ³¹P NMR. [89] At low temperatures, only a single ³¹P NMR signal was observed, consistent with the stability of these complexes at low temperatures in various solvents. However, at the reaction temperature of 120 °C in the presence of 4−7 equiv of triethylamine (with or without iodobenzene), the single ³¹P NMR signal was joined by additional signals. In some cases, palladium black was also formed, providing clear evidence of complex decomposition. In all cases where evidence of decomposition was observed, the triethylamine base was present, suggesting its importance in the process. Additionally, the iminium ion implicated in the mechanism described in Scheme 2 was identified experimentally via mass spectrometry.

The feasibility of the arm-off process was characterized by electronic structure calculations using the BP86 density functional method with a LAC3P/6-31G* basis.[89] These calculations suggested that replacement of one arm of the PCP ligand with an amine base is uphill by about 21 kcal/mol. For the Pd(II)−SCS pincer, the associative displacement of an arm by the amine base was calculated to be uphill by only 7 kcal/mol. These findings were consistent with several

experimental observations including the lack of complex decomposition at low temperatures in the NMR experiments and the necessity for high temperatures (∼120 °C) for Heck coupling reactions when using these precatalysts. While the cursory study of the decomposition mechanism was by no means definitive because many other decomposition paths are also possible, it did suggest one path whereby palladium might be liberated from the tridentate pincer ligand.

Characterizing Polymer- or Silica-"Entrapped" Palladium Salts as Precatalysts in Heck Catalysis

Polymer-Entrapped Pd(OAc)₂, or Pd-EnCat, and the Location of the Active Palladium Species. The application of PVPy as a selective poison for soluble catalytic species was critical to our ability to conclusively show that all catalysis using palladium(II) pincer complexes was associated with palladium(0) species that had been expelled from the ligand.[71,72,89] We thus chose to explore the utility of PVPy and similar poisons in the elucidation of the location of the active species when using other precatalysts where the nature of the catalysis was somewhat ambiguous. Pd-EnCat was purchased from Aldrich and studied using an array of kinetic and poisoning experiments to ascertain the nature of the active species when using this system.

Pd-EnCat has been described as a recyclable, immobilized catalyst system that simplifies removal of palladium from the reaction media after C−C bond forming and reduction processes.[94−97] By applying the use of PVPy and Quadrapure TU[98] (a "palladium sponge" sold by Reaxa Inc., the same firm that developed Pd-EnCat) as solid-phase poisons for leached species in conjunction with standard kinetic and reactivity tests (mercury(0) addition, three-phase tests, recycle tests, etc.[10]), we focused on elucidating whether the catalysis occurs at palladium sites entrapped within the solid matrix or whether, like other supported catalysts (Pd/C, Pd/SiO₂, etc.), these systems represented solids that release palladium into solution, where the catalysis could ultimately occur.[97]

Previously, we used PVPy as a solid poison for soluble catalytic species in our studies of palladium pincer complexes (vide supra). To verify that the poisons PVPy and Quadrapure TU would poison catalysis when using a solid catalyst that is known to operate by leaching active species, we first used these two poisons with a commercial Pd/C precatalyst. It had previously been conclusively shown that this type of precatalyst led to catalysis by exclusively leached, soluble species under similar conditions.[10,19,21−29,99−103] When using

(90) Poverenov, E.; Gandelman, M.; Shimon, L. J. W.; Rozenberg, H.; Ben-David, Y.; Milstein, D. *Chem.−Eur. J.* **2004**, *10*, 4673.
(91) Poverenov, E.; Gandelman, M.; Shimon, L. J. W.; Rozenberg, H.; Ben-David, Y.; Milstein, D. *Organometallics* **2005**, *24*, 1082.
(92) Bassetti, M.; Capone, A.; Salamone, M. *Organometallics* **2004**, *23*, 247.
(93) Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2359.

(94) Lee, C. K. Y.; Holmes, A. B.; Ley, S. V.; McConvey, I. F.; Al-Duri, B.; Leeke, G. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2005**, 2175.
(95) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.; Zhou, W. Z. *Org. Lett.* **2003**, *5*, 4665.
(96) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134.
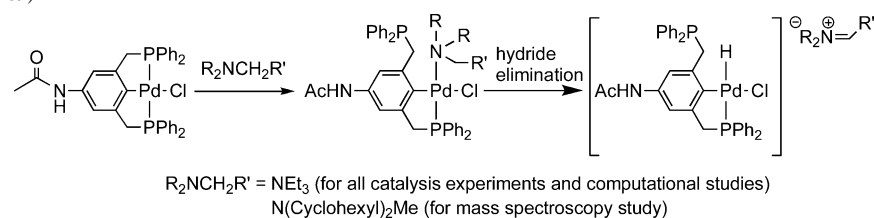(97) Richardson, J. M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 1207.
(98) Andrews, S. P.; Stepan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.* **2005**, *347*, 647.
(99) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, M. *Chem.−Eur. J.* **2002**, *8*, 622.
(100) Köhler, K.; Wagner, M.; Djakovitch, L. *Catal. Today* **2001**, *66*, 105.
(101) Djakovitch, L.; Köhler, K. *J. Mol. Catal. A* **1999**, *142*, 275.

Scheme 2. Initial Steps of a Hypothetical Decomposition Process for Pd(II)−PCP and −SCS Pincer Precatalysts under Heck Reaction Conditions (Reprinted from reference 89)

R$_2$NCH$_2$R' = NEt$_3$ (for all catalysis experiments and computational studies)
N(Cyclohexyl)$_2$Me (for mass spectroscopy study)

Scheme 3. Solid-Phase Poisons for Soluble Catalytic Species Used To Trap Soluble Palladium and Extinguish Solution-Phase Catalysis[a] (Reprinted with permission from reference 97. Copyright Wiley 2006.)
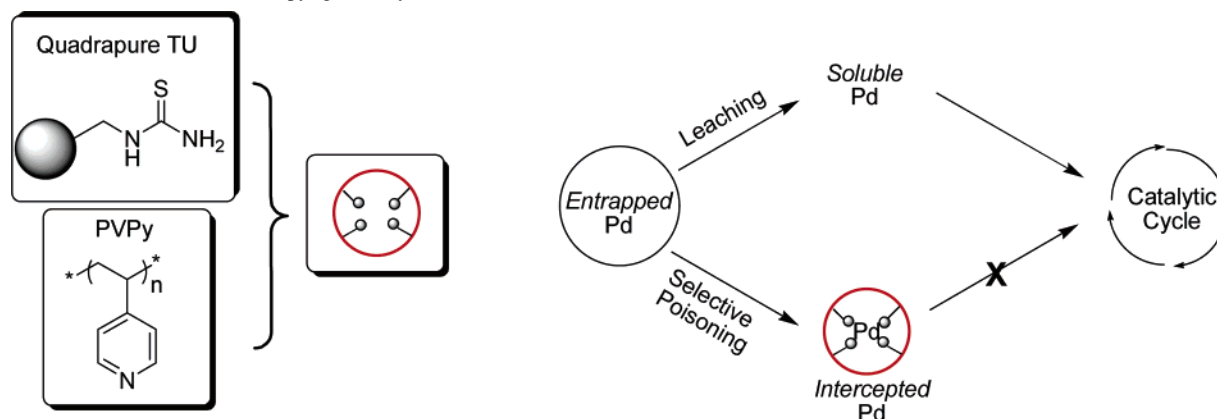
[a] The use of either poison completely extinguished all activity in Heck reactions using Pd-EnCat as a precatalyst, indicating that all catalysis was associated with leached species outside the protective poly(urea) shell.

Pd/C, we were able to show that both solid-phase materials, PVPy and Quadrapure TU, effectively extinguished all catalysis, demonstrating their utility as poisons for soluble active species.[97] Next, we turned our attention to a study of Pd-EnCat.

Using experimental procedures similar to those reported by the original authors, we investigated the use of Pd-EnCat as a precatalyst for Heck coupling reactions of aryl iodides and olefins. As reported earlier, the rates of reaction varied widely with the solvent.[104] Polar, aprotic solvents such as DMF led to rapid catalytic rates, whereas protic solvents such as isopropyl alcohol or aromatic solvents such as toluene led to slower conversions. Interestingly, in all cases, regardless of the solvent, the addition of the solid-phase poisons PVPy or Quadrapure TU in appropriate amounts led to a complete cessation of activity.[97] This observation is consistent with catalysis by palladium that is outside the "protective" poly(urea) matrix used to encapsulate Pd(OAc)$_2$ (Scheme 3). Thus, there is no evidence for catalysis occurring inside the polymer capsules, and Pd-EnCat acts to release active palladium into solution, in much the same way that other solid-phase precatalysts behave. Our results suggest that the varying rates of reaction observed using Pd-EnCat in different solvents are associated with the propensity of the different media for stabilizing the active, leached palladium species.[97]

It should be noted that, after submission of our work, a careful, comprehensive study by Broadwater and McQuade appeared that reached similar conclusions with regard to

leaching of palladium from other Pd-EnCat precatalysts under Heck and Suzuki conditions.[105] Using three-phase tests and transmission electron microscopy analysis, they showed that leaching of catalytically active palladium was occurring, but they could not determine whether any catalysis was occurring inside the Pd-EnCat matrixes. The absence of such activity was demonstrated in our work.[97] It is suggested that PVPy, Quadrapure TU, or other solid-phase poisons[36,106] might be useful in the determination of the location of the active species when using other new precatalysts that use an encapsulation strategy because in many cases the existing data leave the location of the catalysis somewhat ambiguous.[10,107−110]

Toward Stable, Supported, Recoverable, and Recyclable Palladium Heck Catalysts

Poly(norbornene)-Tethered Palladium(II) N-Heterocyclic Carbene (NHC) Complexes. With the failure of the SCS and PCP pincer ligands to provide stable, immobilizable metal−ligand complexes for Heck coupling, alternative ligand systems were considered, and the NHC system was chosen for further study. Stable NHCs were first synthesized by Arduengo et al., and since this time, they have been
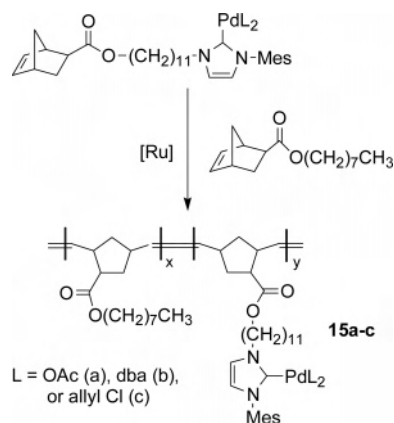
(102) Zhao, F. Y.; Arai, M. *React. Kinet. Catal. Lett.* **2004**, *81*, 281.
(103) Djakovitch, L.; Köhler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990.
(104) *Chemfiles* **2004**, *4*, 1.

(105) Broadwater, S. J.; McQuade, D. T. *J. Org. Chem.* **2006**, *71*, 2131.
(106) Guino, M.; Hii, K. K. M. *Tetrahedron Lett.* **2005**, *46*, 6911.
(107) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375.
(108) Martinez, S.; Vallribera, A.; Cotet, C. L.; Popovici, M.; Martin, L.; Roig, A.; Moreno-Manas, M.; Molins, E. *New J. Chem.* **2005**, *29*, 1342.
(109) Cho, J. K.; Najman, R.; Dean, T. W.; Ichihara, O.; Muller, C.; Bradley, M. *J. Am. Chem. Soc.* **2006**, *128*, 6276.
(110) Yang, Q.; Ma, S. M.; Li, J. X.; Xiao, F. S.; Xiong, H. *Chem. Commun.* **2006**, 2495.

studied extensively because of the outstanding stability of many NHC/metal complexes.[111] NHC ligands have a number of advantages over the closely related phosphine ligands, in particular increased stability to high temperatures and air. Therefore, palladium precatalysts for coupling reactions based on these ligands have been extensively reported over the past 10 years.[112−132]

Supported precatalysts based on NHC ligands were first investigated by Herrmann and co-workers, who reported the use of bidentate NHC ligands complexed to palladium(II) species on Wang resins as supports.[112] Since then, other authors have reported Pd−NHC complexes on both poly-meric[133−143] and oxide[144−153] supports. In many cases, the

Scheme 4. Copolymerization via ROMP of a Pd−NHC-Containing Norbornene Monomer with an Norbornyl Octanoate Spacer Monomer To Produce Soluble, Supported Precatalyst **15** [**a** = Pd(OAc); **b** = PdCl; **c** = Pd(dba)] (Reprinted with permission from reference 154. Copyright Wiley 2006.)

supported complexes have been shown to leach inactive or active palladium species,[153] although in some cases the possibility of catalyst decomposition was not assessed.

Following the approach described above for the development of supported palladium pincer complexes, we again employed soluble polymers as supports and tethered the NHC ligands onto the polymer side chains. In particular, we employed the same basic polymer structure and polymerization method for these studies as described above for the polymer-supported Pd−SCS and −PCP pincer studies, poly-(norbornene)s and ring-opening metathesis polymerization (ROMP). In close analogy to the above-described polymer-supported palladium(II) pincer complexes, we synthesized a series of poly(norbornene) copolymers containing Pd−NHC complexes, stemming from the reaction of the NHC norbornene monomer with Pd(OAc)$_2$, Pd$_2$(dba)$_3$, or Pd$_2$(allyl)$_2$-Cl$_2$, along the side chains (Scheme 4).[154]

We evaluated the catalytic activities of these supported palladium complexes in the Suzuki−Miyaura, Sonogashira, and Heck coupling reactions (Suzuki, aryl chlorides or bromides and phenylboronic acid, 80 °C; Sonogashira, aryl bromides and phenylacetylenes, 25−80 °C; Heck, iodoben-zene and *n*-butyl acrylate, 120 °C; see previous publication[154] for bases used and further experimental details). In all cases, the polymeric catalysts demonstrated a similar activity compared to their small-molecule analogues.[154] Furthermore,

(111) Arduengo, A. J.; Dias, H. V. R.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1992**, *114*, 9724.
(112) Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem.−Eur. J.* **2000**, *6*, 1773.
(113) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23.
(114) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93.
(115) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348.
(116) Herrmann, W. A.; Böhm, V. P. W.; Gstottmayr, C. W. K.; Grosche, M.; Reisinger, C. P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617*, 616.
(117) Herrmann, W. A.; Ofele, K.; Von Preysing, D.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229.
(118) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031.
(119) Böhm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186.
(120) Frisch, A. C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal. A* **2004**, *214*, 231.
(121) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.
(122) Grasa, G. A.; Viciu, M. S.; Huang, J. K.; Zhang, C. M.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.
(123) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173.
(124) Zhang, C. M.; Huang, J. K.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804.
(125) Navarro, O.; Oonishi, Y.; Kelly, R. A.; Stevens, E. D.; Briel, O.; Nolan, S. P. *J. Organomet. Chem.* **2004**, *689*, 3722.
(126) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C. L.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.
(127) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815.
(128) Pytkowicz, J.; Roland, S.; Mangeney, P.; Meyer, G.; Jutand, A. *J. Organomet. Chem.* **2003**, *678*, 166.
(129) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741.
(130) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596.
(131) McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165.
(132) Magill, A. M.; McGuinness, D. S.; Cavell, K. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; White, A. H.; Skelton, B. W. *J. Organomet. Chem.* **2001**, *617*, 546.
(133) Steel, P. G.; Teasdale, C. W. T. *Tetrahedron Lett.* **2004**, *45*, 8977.
(134) Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2004**, *45*, 1837.
(135) Kim, J. H.; Jun, B. H.; Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2004**, *45*, 5827.
(136) Kim, J. H.; Kim, J. W.; Shokouhimehr, M.; Lee, Y. S. *J. Org. Chem.* **2005**, *70*, 6714.
(137) Shokouhimehr, M.; Kim, J. H.; Lee, Y. S. *Synlett* **2006**, 618.
(138) Zhang, S. J.; Zeng, X. M.; Wei, Z. J.; Zhao, D. B.; Kang, T. R.; Zhang, W. F.; Yan, M.; Luo, M. M. *Synlett* **2006**, 1891.
(139) Schönfelder, D.; Fischer, K.; Schmidt, M.; Nuyken, O.; Weberskirch, R. *Macromolecules* **2005**, *38*, 254.
(140) Schönfelder, D.; Nuyken, O.; Weberskirch, R. *J. Organomet. Chem.* **2005**, *690*, 4648.
(141) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Karbass, N.; Luis, S. V.; Puzary, A.; Sans, V. *Tetrahedron Lett.* **2006**, *47*, 2311.
(142) Kang, T. R.; Feng, Q.; Luo, M. M. *Synlett* **2005**, 2305.
(143) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Synlett* **2005**, 3116.
(144) Karbass, N.; Sans, V.; Garcia-Verdugo, E.; Burguete, M. I.; Luis, S. V. *Chem. Commun.* **2006**, 3095.
(145) Poyatos, M.; Marquez, F.; Peris, E.; Claver, C.; Fernandez, E. *New J. Chem.* **2003**, *27*, 425.
(146) Mas-Marza, E.; Segarra, A. M.; Claver, C.; Peris, E.; Fernandez, E. *Tetrahedron Lett.* **2003**, *44*, 6595.
(147) Zhao, Y. H.; Zhou, Y. Y.; Ma, D. D.; Liu, J. P.; Li, L.; Zhang, T. Y.; Zhang, H. B. *Org. Biomol. Chem.* **2003**, *1*, 1643.
(148) Stevens, P. D.; Fan, J. D.; Gardimalla, H. M. R.; Yen, M.; Gao, Y. *Org. Lett.* **2005**, *7*, 2085.
(149) Stevens, P. D.; Li, G. F.; Fan, J. D.; Yen, M.; Gao, Y. *Chem. Commun.* **2005**, 4435.
(150) Karimi, B.; Enders, D. *Org. Lett.* **2006**, *8*, 1237.
(151) Aksin, O.; Turkmen, H.; Artok, L.; Cetinkaya, B.; Ni, C. Y.; Buyukgungor, O.; Ozkal, E. *J. Organomet. Chem.* **2006**, *691*, 3027.
(152) Zheng, Y.; Stevens, P. D.; Gao, Y. *J. Org. Chem.* **2006**, *71*, 537.
(153) Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2006**, in press.
(154) Sommer, W. J.; Weck, M. *Adv. Synth. Catal.* **2006**, *348*, 2101.

we found the same trend for the employment of activated and deactivated arenes as described in the literature. While electron-withdrawing groups increase the reaction kinetics, electron-donating groups slow down the conversions.[155−157] Given that previous authors reported some instability when using supported Pd−NHC precatalysts in coupling reactions, the stability of our polymer-supported systems was identified as a key issue to probe. Early on, it was clear that all supported catalysts are not stable during the Heck reaction conditions. Significant leaching of palladium from the supports occurred while carrying out the Heck coupling of iodobenzene with *n*-butyl acrylate based on the palladium black detected.[153,154] In contrast, no palladium black formation was evident when carrying out Suzuki−Miyaura and Sonogashira coupling reactions. Therefore, the stability of the precatalysts was probed in these chemistries using kinetic and leaching/poisoning tests as described above for the palladium(II) pincer systems. For these leaching tests, three different poisons were used, PVPy, mercury(0), and Quadrapure TU. When carrying out the PVPy poisoning test at a ratio of 1:500 of Pd to PVPy using precatalyst **15a** [Pd-(OAc)−NHC], we observed a decrease in activity with only 15% total conversion after 24 h.[154] However, the catalyst remained active during the whole experiment. To test if this productivity decrease was due to palladium leaching off the supported NHC ligands or due to the lack of accessibility of the reactants to the catalyst sites (because the addition of PVPy visibly increased the viscosity of the solution since very little solvent was used), we carried out the same reaction using cross-linked poly(styrene) as a non-palladium-coordinating viscosity modifier ($M_W = 25\,000$). In the presence of 500 equiv of poly(styrene) for each catalytic moiety, we again observed a significant drop in the catalyst activity with a conversion of approximately 15% after 24 h. This observation suggests in this case that the reduced activity in the PVPy leaching test was most likely not due to metal leaching during the catalysis but instead to reduced accessibility of the active sites in this case.[153,154] This is an important subtlety in the application of this poison to soluble polymeric precatalysts that complicates its use.

Further poisoning studies using Quadrapure TU showed that both precatalysts **15a** [Pd(OAc)−NHC] and **15c** [Pd-(Cl)−NHC] showed significant activity in the presence of each poison. However, the rates were somewhat suppressed compared to conditions that lacked an added poison. Unlike PVPy, the amount of Quadrapure TU used did not cause significant viscosity effects in these reactions. The observed catalytic activity in the presence of this poison suggests that each precatalyst may become an active, immobilized palladium catalyst under the conditions used.[154] It should be noted that these reactions where some active, immobilized molecular catalyst *might* exist are carried out under low-temperature conditions,[11,12] between room temperature and

80 °C. However, relatively low amounts of poison were used (2 mol of poison to 1 mol of palladium), and the reactivity may be fully extinguished at higher poison levels. It is further possible that the decreased rates are due to some poisoning of leached active species or simply decreased accessibility of the reagents to the catalytic sites in the multiphase media created by the added poisons. Additional studies are needed to elucidate these trends.

In contrast, the poisoning and kinetic studies show that the precatalyst **15b** [Pd(dba)−NHC] likely leaches under the Suzuki−Miyaura and Sonogashira reaction conditions because Quadrapure TU is an effective poison for this precatalyst, effectively shutting down activity. Thus, in this case, the catalytic species is a leached palladium species, and the supported complex **15b** served only as a palladium reservoir.[154]

Strategies for Assessing the Nature of the Reactive Species in Palladium-Mediated Coupling Reactions

Despite the importance of the palladium-catalyzed Heck, Suzuki, Sonogashira, Stille, and other C−C bond forming reactions, the nature of the truly active catalytic species in most cases is not well-established. Indeed, as noted above, for the Heck coupling, virtually every form of palladium known has been suggested to be an active catalyst, from supported palladium metal particles, to soluble palladium nanoparticles, to metal−ligand complexes. More often than not, authors simply assume or assert that the form of the palladium that they add to the reaction is the active catalyst.

To this end, a comprehensive review of palladium-catalyzed Heck and Suzuki coupling chemistry with an eye toward identifying the nature of the truly active form of palladium was recently published.[10,158] The collected data are consistent with only catalysis by a Pd(0)−Pd(II) cycle, regardless of the precatalyst used, and no experimental evidence exists to support a Pd(II)−Pd(IV) cycle. The data are also consistent with catalysis occurring via a common catalytic mechanism when high temperatures[12] are used. Recently, de Vries analyzed and summarized numerous reports of Heck catalysis at high temperatures using various precatalysts.[11] The collected data are consistent with catalysis by molecular palladium species that are in equilibrium with solvated palladium nanoparticles. At lower temperatures, there is clear evidence that specific ligands can effect changes in catalytic activity and selectivity, for example, allowing for the conversion of aryl chlorides and facilitating enantioselective Heck catalysis.[10]

There is, however, no compelling, definitive evidence for complete catalytic turnovers on a palladium metal particle surface in either Heck or Suzuki coupling reactions. The collected evidence to date clearly supports the oxidative addition of aryl halides (especially iodides) to the surface

(155) Yang, C. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.
(156) Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194.
(157) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

(158) This comprehensive review[10] of the nature of the catalytic species for palladium-mediated Heck and Suzuki reactions was inspired by a similar comprehensive review published by Widegren and Finke on distinguishing between homogeneous and heterogeneous catalysis.[159] Our review in many ways is an extension of their previous publication with a focus on palladium chemistry.
(159) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A* **2003**, *198*, 317.

of palladium(0) particles.[10] However, it is suggested that this leads to dissolution of the palladium(II) aryl iodo species into solution, where the final part of the catalytic cycle, insertion of the olefin, occurs.[10,11] Subsequent catalytic turnover with the solvated palladium(0) regenerated after one cycle is then suggested to occur. Although solid catalyzed Heck coupling reactions continue to be claimed in the literature, no one to date has shown definitive data supporting their existence.[10]

Because so few authors take the time to assess the nature of the true catalytic species in a rigorous way, we outlined a collection of techniques that can be used together to shed light on the nature of the true catalyst. Several of these methods have been discussed above in our evaluation of catalysis via palladium pincer precatalysts. They include mercury(0) poisoning, kinetic tests, three-phase tests, filtration or split tests, and use of various soluble and insoluble catalyst poisons. The full scope of these various tests is described in detail in our previous publication.[10] Increasingly, some authors are using such a diverse array of catalytic tests to ascertain the nature of the true catalytic species in coupling chemistries.[58,151,160−162]

Intriguing Catalytic Systems Worth Further Study

In this final section, we highlight a few precatalysts that stand out as warranting further study. For instance, there are a number of recently reported immobilized metal complex catalysts where the nature of the active species is somewhat ambiguous based on the data presented.[10,141,148,149,152,163−169] These systems represent ideal targets for the approach described here of combining multiple kinetic and poisoning tests to elucidate the location of the truly active species.

Whereas nearly all palladacycle precatalysts (including pincers[37−45,64−73,86,88,89,170−175]) likely decompose under reaction conditions to liberate ligand-free catalytic species under high-temperature conditions,[12] there are two classes of palladacycle complexes that appear to exhibit unique reactivity. The first class is the oxime palladacycles extensively developed by Najera et al.[176] Although it has been hypothesized that all palladacycles operate by a mechanism in common with "naked" palladium salts at high temperatures,[10,11] it is interesting that the oxime carbapalladacycles, while clearly decomposing under reaction conditions to form palladium nanoparticles,[176] are still able to convert aryl chlorides that are usually unreactive when using preformed palladium nanoparticles under similar conditions. This warrants further investigation, and a reasonable hypothesis has been put forth by Corma et al., who postulate that intact palladium(0) oxime carbapalladacycles that have not yet decomposed are active for this process.[177]

The second class of palladacycle precatalysts worth highlighting for further study are the CNC type pincer palladium(II) complexes (Figure 1, complex **2b**).[141,178−182] These palladium(II) complexes, like the SCS, PCP, and NCN pincer complexes that preceded them, have been described as completely stable complexes that may operate by a Pd-(II)−Pd(IV) mechanism. Indeed, these precatalysts appear to be the last bastion of hope for proponents of the Pd(II)−Pd(IV) cycle,[182] owing to a reported activity in the presence of mercury(0),[179,180,183] a validated stability at high temperatures in various solvents, and a perceived stability under reaction conditions.[181] It would be intriguing to use the full array of tests[10] available to determine if complexes of this type operate via a classical Pd(0)−Pd(II) catalytic cycle or a hypothesized Pd(II)−Pd(IV) cycle and, furthermore, if the catalysis occurs at a palladium center bound by the CNC ligand or at a "naked"[32] palladium species.

Concluding Remarks

We began our investigations into palladium-catalyzed coupling chemistry in 2003 with an interest in the design of stable, supported molecular palladium complex catalysts. Starting with studies of the Pd(II)−SCS pincer system of precatalysts, we systematically showed that these precatalysts decompose to form solution-phase, pincer-ligand-free active species. By applying an array of kinetic and poisoning tests to both supported and unsupported precatalysts, we were able to conclusively rule out for the first time the contribution of the hypothetical Pd(II)−Pd(IV) cycle to Heck catalysis when using pincer palladacyclic precatalysts. We subsequently showed that a myriad of different SCS and PCP pincer precatalysts all decomposed to give soluble palladium(0) catalysts. A key technique that enabled our conclusions was

(160) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133.
(161) Dell'Anna, M. M.; Lofu, A.; Mastrorilli, P.; Mucciante, V.; Nobile, C. F. *J. Organomet. Chem.* **2006**, *691*, 131.
(162) Crudden, C. M.; Sateesh, M.; Lewis, R. *J. Am. Chem. Soc.* **2005**, *127*, 10045.
(163) Xu, X.; Liu, P.; Li, S. H.; Zhang, P.; Wang, X. Y. *React. Kinet. Catal. Lett.* **2006**, *88*, 217.
(164) Zhou, R. X.; Zhou, J. M.; Zheng, X. M. *React. Kinet. Catal. Lett.* **2005**, *87*, 157.
(165) Blanco, B.; Brissart, M.; Moreno-Manas, M.; Pleixats, R.; Mehdi, A.; Reye, C.; Bouquillon, S.; Henin, F.; Muzart, J. *Appl. Catal. A* **2006**, *297*, 117.
(166) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065.
(167) Gil-Molto, J.; Karlstrom, S.; Najera, C. *Tetrahedron* **2005**, *61*, 12168.
(168) Choudary, B. M.; Roy, M.; Roy, S.; Kantam, M. L.; Sreedhar, B.; Kumar, K. V. *Adv. Synth. Catal.* **2006**, *348*, 1734.
(169) Cai, M. Z.; Xu, Q. H.; Wang, P. P. *J. Mol. Catal. A* **2006**, *250*, 199.
(170) Yao, Q. W.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997.
(171) Takenaka, K.; Uozomi, Y. *Adv. Synth. Catal.* **2004**, *346*, 1693.
(172) Jung, I. G.; Son, S. U.; Park, K. H.; Chung, K.-C.; Lee, J. W.; Chung, Y. K. *Organometallics* **2003**, *22*, 4715.
(173) Díez-Barra, E.; Guerra, J.; Hornillos, V.; Merino, S.; Tejeda, J.; *Organometallics* **2003**, *22*, 4610.
(174) Nilsson, P.; Wendt, O. F. *J. Organomet. Chem.* **2005**, *690*, 4197.
(175) Olsson, D.; Nilsson, P.; El Masnaouy, M.; Wendt, O. F. *Dalton Trans.* **2005**, 1924

(176) Alacid, E.; Alonso, D. A.; Botella, L.; Najera, C.; Pacheco, M. C. *Chem. Rec.* **2006**, *6*, 117.
(177) Corma, A.; Garcia, H.; Leyva, A. *J. Catal.* **2006**, *240*, 87.
(178) Loch, J. A.; Albrecht, M.; Peris, E.; Mata, J.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700.
(179) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239.
(180) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201.
(181) Churruca, F.; SanMartin, R.; Ines, B.; Tellitu, I.; Dominguez, E. *Adv. Synth. Catal.* **2006**, *348*, 1836.
(182) Hahn, F. E.; Jahnke, M. C.; Gomez-Benitez, V.; Morales-Morales, D.; Pape, T. *Organometallics* **2005**, *24*, 6458.
(183) It is noteworthy that the related nickel(II) complexes are poisoned by mercury(0). Inamoto, K.; Kuroda, J.-I.; Hiroya, K.; Noda, Y.; Watanabe, M.; Sakamoto, T. *Organometallics* **2006**, *25*, 3095.

the application of palladium scavengers to selectively poison catalysis by leached species. We later then used this technique to assess the location of the active species when using a commercial poly(urea)-encapsulated $Pd(OAc)_2$ pre-catalyst, showing that all catalysis was associated with leached species outside the polymer matrix. In general, all of the immobilized precatalysts we have tested under high-temperature conditions[12] decompose to generate leached, soluble active palladium(0) species, consistent with literature precedents.[10,11] It is strongly suggested that all authors who develop a new palladium precatalyst for coupling reactions assess the nature of the truly active species by employing a combination of tests described here and in our previous comprehensive review.[10] Our research on immobilized forms of palladium for coupling reactions continues, with our initial investigations of polymer-supported Pd−NHC complexes summarized here. Additional studies focusing on the assessment of the location of the active species when using a variety of different precatalysts in coupling reactions continue as well.