Ionophilic phosphonium-appended carbopalladacycle catalyst for Suzuki–Miyaura and Heck cross-coupling catalysis

Jocelyn J. Tindale and Paul J. Ragogna

Abstract: An ionic liquid, covalently tethered to an efficient transition-metal catalyst in the presence of an ionic liquid reaction medium, can utilize ionophilic interactions to improve catalyst activity, recyclability, and product isolation while decreasing catalyst leaching. Given the greater stability of phosphonium salts in comparison to imidazolium ionic liquids under basic conditions, phosphonium-tagged oxime carbopalladacycle salts were prepared and employed in both Heck and Suzuki–Miyaura reactions. The desired product was obtained in good yields for up to four catalyst cycles in the case of the Suzuki–Miyaura reaction. While taking advantage of the non-volatile nature of ionic liquids, the product was isolated through simple sublimation from the reaction mixture, eliminating issues associated with catalyst leaching, and the remaining ionic liquid solvent–catalyst mixture was ready for further catalysis.

Key words: phosphonium, ionic liquids, ionophilic catalysis, carbopalladacycle, ionic tag.

Résumé : Un liquide ionique lié d’une façon covalente à un catalyseur efficace à base d’un métal de transition, en présence d’un milieu réactionnel formé d’un liquide ionique, peut utiliser les interactions ionophiles pour améliorer l’activité du catalyseur, sa capacité à être recyclé et la facilité d’isoler le produit tout en diminuant la lixiviation du catalyseur. Se basant sur la plus grande stabilité des sels de phosphonium par comparaison aux liquides ioniques à base d’imidazolium dans des conditions basiques, on a préparé des sels à base carbocycles contenant du palladium sels et portant des phosphonium d’oximes comme étiquette ionique et on les a utilisés dans des réactions de Heck et de Suzuki–Miyaura. Le produit désiré a été obtenu avec de bons rendements pour au moins quatre cycles catalytiques dans le cas de la réaction de Suzuki–Miyaura. En tirant avantage de la nature non volatile des liquides ioniques, on a pu isoler le produit par simple sublimation à partir du milieu réactionnel, éliminant ainsi les problèmes associés avec la lixiviation du catalyseur et alors que le mélange solvant liquide ionique/catalyseur est prêt à être réutilisé pour d’autres réactions catalytiques.

Mots-clés : phosphonium, liquides ioniques, catalyse ionophile, carbocycles contenant du palladium, marquage ionique.

[Traduit par la Rédaction]

Introduction

The use of ionic liquids (ILs) as an alternative solvent in catalysis has become popular over the last ten years as a means of rendering the reaction “green”.[1] This notion predominantly stems from the ionic nature of the salts, which give rise to a negligible vapor pressure. However, given recent reports on the toxicity of some ILs, their potential application as “green” solvents has faltered.[2,3] Nevertheless, many of their properties beyond non-volatility do render these materials highly amenable to many chemical reactions and applications. High thermal stabilities, wide liquid temperature ranges, and unique solubility parameters give rise to ionic liquids as good alternative solvents. Ionic liquids generally have the ability to dissolve many organic and organometallic compounds and are often immiscible with non-polar organic solvents.[4] The breadth of potential applications is further amplified given the general framework of common ionic liquids, such as imidazolium or pyridinium salts, is susceptible to chemical modification to attain a desired function while concomitantly maintaining the intrinsic properties of the low melting salts.

The ease of dissolution of transition metals in ionic liquids and the immiscibility observed with some organic solvents are both phenomena associated with ionic liquids that are often exploited in catalysis. These properties enable an improvement in the isolation of the organic product from the catalyst during simple extraction procedures.[5,6] Unfortunately, in some cases, the catalyst activity quickly decreases after several runs.[7] This is often a result of catalyst leaching during the extraction of the product from the reaction mixture or in the purification of the ionic liquid before the initiation of the next reaction cycle. To ensure retention of the catalyst within the ionic liquid phase and consequently improve the recyclability of the system and the isolation of products, modifications to the catalyst are required. A current methodology includes preparing a catalyst that mimics the physico-chemical properties of the ionic medium, thus increasing the ionophilicity of the catalyst. Shreeve et al. have synthesized a (carbene)palladium(II) catalyst that resembles the skeletal structure of the imidazolium ionic liquid reaction medium and was used successfully to facili-

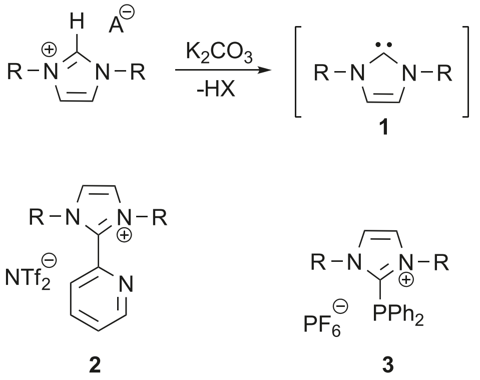
Received 21 August 2009. Accepted 5 October 2009. Published on the NRC Research Press Web site at canjchem.nrc.ca on 17 December 2009.

J.J. Tindale and P.J. Ragogna.[1] Department of Chemistry, The University of Western Ontario, 1151 Richmond St, London, ON, N6A 5B7, Canada.

[1] Corresponding author (e-mail: pragogna@uwo.ca).

doi:10.1139/V09-149

Chart 1. Illustration of the decomposition of an imidazolium cation in the presence of base resulting in the formation of a carbene, **1**, and alternative imidazolium cations protected at the C-2 position, **2** and **3**.



tate C–C bond forming reactions.[8,9] A more prevalent strategy to increase a catalyst's ionophilicity is to covalently integrate an ionic fragment into the catalyst framework. A critical review highlighting various successes employing ionic liquid ligands for the preparation of ionophilic catalysts has recently been published.[10,11]

Carbon–carbon bond forming reactions, such as Heck and Suzuki–Miyaura, are some of the most important reactions in organic synthesis. Substantial effort has been put forth to convert the successful homogeneous methodology into a heterogeneous system with enhanced catalyst recyclability. Recently, ionophilic ionic-liquid-tagged catalysts have been reported as a means of achieving this goal.[12,13] The ubiquitous imidazolium cation has been employed as an ion tag; however, it is susceptible to degradation under basic conditions, a requirement for the Heck and Suzuki–Miyaura reactions. The subsequent formation of a carbene, **1**, leads to poor yields, unwanted side-products, and inactive catalysts.[14–16] One approach to avoid this problem is the substitution of a metal-binding ligand such as a pyridine, **2**, or phosphine, **3**, at the C-2 position on the imidazolium cation (Chart 1).[17,18]

Our methodology, inspired by the work of Corma et al.,[19] also evades the susceptibility of imidazolium salts towards decomposition in the presence of base. Utilizing the ionophilic ionic-liquid-appended catalyst concept, a phosphonium salt was tethered to an oxime carbopalladacycle moiety, which was previously noted as an exceptional catalyst for Suzuki–Miyaura cross-coupling of aryl halides and arylboronic acids.[20,21] Phosphonium salts do not share the same vulnerability to basic conditions as observed for imidazolium cations and have been successfully used as alternative solvent media in Suzuki and Heck reactions without any signs of decomposition products such as Wittig-type reagents.[22–26] In this context, a phosphonium-tagged oxime carbopalladacycle catalyst precursor **8** has been synthesized and comprehensively characterized. It is important to note here that Singer et al. have prepared similar ionophilic ligands derived from oximes with pendant imidazolium salts. The salts were designed as capturing devices for sequestering metals from aqueous solutions, and their use as cross-coupling pre-catalysts was not investigated.[27] Herein, cross-coupling reactions catalyzed by the ionophilic catalyst, **8**, were conducted using trihexyltetradecylphosphonium chloride, [P$_{66614}$][Cl], as the reaction medium. Increased isolated yields and catalyst recyclability were noted as significant improvements to previous reports of ionophilic oxime carbopalladacycle cross-coupling catalysis.

Experimental section

Materials

The solvents were obtained from Caledon Laboratories. Dichloromethane, *N*,*N*-dimethylformamide, and toluene were dried using an Innovative Technologies Inc. Solvent Purification System, which utilizes dual-alumina columns, and were stored under a nitrogen or argon atmosphere in Strauss flasks or stored in the glovebox over 4 Å molecular sieves. Methanol was dried by storing over 3 Å molecular sieves. The trihexyltetradecylphosphonium chloride (Strem), styrene (Aldrich), *p*-methoxyphenyl boronic acid (Aldrich), and iodobenzene (Aldrich) were used as received and stored in a nitrogen-filled MBraun Labmaster 130 glovebox. The palladium dichloride (Pressure Chemicals), K$_3$PO$_4$ (Riedel-deHaën), and LiCl (Caledon) were used as received and stored in a desiccator. Deuterated NMR solvents (CDCl$_3$, DMSO) were purchased from Cambridge Isotope Laboratories and were stored over 4 Å molecular sieves. Tri-*n*-butyl phosphine was generously donated by Cytec Industries and was distilled prior to use. Manipulations involving the use of ^{n}Bu$_3$P and the catalysis experiments were performed either in the glovebox or by using standard Schlenk techniques. The precursors 4-hydroxyacetophenone oxime and 4-(5-bromopentoxy)acetophenone oxime were synthesized using literature methods.[19]

Measurements

Solution ^{1}H, ^{31}P{^{1}H} and ^{13}C{^{1}H}, gHMBC, and gHSQC NMR spectra were recorded on a Varian INOVA 400 MHz, Varian INVOA 600 MHz, or Mercury 400 MHz spectrometer. All samples for ^{1}H NMR, ^{13}C{^{1}H}, gHMBC, and gHSQC spectroscopy were referenced to the residual protons in the solvent relative to (CH$_3$)$_4$Si (δ (ppm); ^{1}H: CDCl$_3$ 7.26, DMSO 2.50; ^{13}C{^{1}H}: CDCl$_3$ 77.0, DMSO 39.52). Phosphorus-31 NMR chemical shifts were reported relative to an external standard (85% H$_3$PO$_4$ $\delta = 0.00$ ppm). Mass spectrometry measurements were recorded in positive and negative ion modes using an electrospray ionization Micromass LCT spectrometer. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada.

The decomposition temperatures were determined using thermogravimetric analysis (TGA) on a Q600 SDT TA Instrument for **7** or on a TGA/SDTA 851e Mettler Toledo instrument for **8**. A 0.005–0.010 g sample was heated in a 40 µL alumina crucible at a rate of 10 °C/min over a temperature range of 100–600 °C. Melting and glass transition points were determined using differential scanning calorimetry (DSC) on a Q20 DSC TA instrument for **7** or on a DSC 822^e Mettler Toledo instrument for **8** using aluminum sample pans. For **7**, a 0.005–0.010 g sample was cooled to –90 °C and then heated to 200 °C at 10 °C/min, cooled to –90 at 10 °C/min, and finally reheated to 200 °C at 10 °C/min. The glass-transition temperatures were taken from the final heat cycle. For **8**, a 0.005–0.010 g sample was cooled to –70 °C where the temperature was sustained for 15 min, followed by heating to 500 °C at 10 °C/min. All thermal analysis experiments were conducted in a $N_{2(g)}$ atmosphere.

Synthesis

Preparation of 7

To a solution of 4-(5-bromopentoxy)acetophenone oxime (0.970 g, 3.220 mmol) in DMF (17 mL) ^{n}Bu$_3$P (0.716 g, 3.542 mmol) was added, and the mixture was heated at 70 °C for 48 h under a flow of nitrogen. DMF was removed in vacuo, and the resulting viscous yellow liquid was dissolved in a minimal amount of CH_2Cl_2, which was extracted first with hexanes (2 × 15 mL) and then with THF (1 × 15 mL). The residual solvent was removed in vacuo yielding **7** as a viscous clear yellow liquid (1.083 g, 2.155 mmol, 67%). T_d = 343 °C; T_g = –2 °C. ^{31}P{^{1}H} NMR (161.96 MHz, $CDCl_3$) δ (ppm): 30 (s). ^{1}H NMR (599.69 MHz, $CDCl_3$) δ (ppm): 7.57 (d, 2H, ^{3}J = 9.0 Hz), 7.42 (s, br, 1H), 6.86 (d, 2H, ^{3}J = 8.4 Hz), 4.00 (t, 2H, ^{3}J = 6.0 Hz), 2.60–2.55 (m, 2H), 2.48–2.43 (m, 6H), 2.25 (s, 3H), 1.87 (quintet, 2H, ^{3}J = 6.6 Hz), 1.74–1.64 (m, 4H), 1.56–1.51 (m, 12H), 0.97 (s, 9H). ^{13}C{^{1}H} NMR (100.60 MHz, $CDCl_3$) δ (ppm): 159.2, 153.6, 129.1, 126.8, 113.9, 67.2, 28.2, 27.1 (d, $^{3}J_{P\text{–}C}$ = 13 Hz), 23.5 (d, $^{3}J_{P\text{–}C}$ = 12 Hz), 23.4 (d, $^{2}J_{P\text{–}C}$ = 3 Hz), 21.3 (d, $^{2}J_{P\text{–}C}$ = 4.6 Hz), 19.1 (d, $^{1}J_{P\text{–}C}$ = 47.5 Hz), 18.7 (d, $^{1}J_{P\text{–}C}$ = 47.0 Hz), 13.2, 11.6. FTIR (dropcast on KBr; cm^{-1}(ranked intensity)): 510(20), 561(14), 634(12), 725(11), 838(3), 924(4), 1006(7), 1094(16), 1182(9), 1250(1), 1304(10), 1376(15), 1464(8), 1515(6), 1610(5), 1673(21), 2870(17), 2959(2), 3169(13), 3207(19), 3263(18). MS (ESI) $m/z^{+/-}$ (%): 422.3 (100) [M^{+} – Br], 923.6^{5} [M$_2$Br^{+}], 582.2 (35) [MBr$_2$].

Preparation of 8

The Li_2PdCl_4 was first prepared by the addition of $PdCl_2$ (0.212 g, 1.193 mmol) to a solution of LiCl (0.101 g, 2.387 mmol) in MeOH (0.6 mL), which was then heated at 60 °C for 30 min until all the reagents dissolved. Sodium acetate (0.049 g, 0.597 mmol) and **7** (0.300 g, 0.597 mmol) in MeOH (0.65 mL) were then added dropwise to the resulting red methanolic Li_2PdCl_4 solution, and the mixture was stirred at room temperature for 36 h. Methanol was then added (2 mL), and the heterogeneous mixture was centrifuged and the supernatent was decanted. The solids were washed with MeOH (4 × 4 mL) followed by acetone (4 × 4 mL) to selectively remove the red-brown solid. The acetone fractions were combined and cooled to –30 °C. Upon precipitation of a beige solid, the mixture was centrifuged, the supernatent was removed, and the solid was dried in vacuo giving **8** as a beige powder (0.144 g, 0.112 mmol, 19%). T_d = 290 °C; T_m = 160 °C. ^{31}P{^{1}H} NMR (161.96 MHz, $CDCl_3$) δ (ppm): 30 (s). ^{1}H NMR (400.09 MHz, DMSO) δ (ppm): 10.5 (s, br,1H), 7.17 (s, br, 1H), 7.06 (d, 2H, ^{3}J = 8.4 Hz), 6.54 (d, 2H, ^{3}J = 8.4 Hz), 3.93 (t, 2H, ^{3}J = 6.4 Hz), 2.22–2.15 (m, 11H), 1.73 (quintet, 2H, ^{3}J = 6.0 Hz), 1.53–1.35 (m, 16H), 0.90 (t, 9H, ^{3}J = 6.8 Hz). ^{13}C{^{1}H}/gHSQC/gHMBC (599.44 MHz, DMSO) δ (ppm): 163.4, 157.5, 153.6, 138, 129, 120.8, 109.5, 66.8, 27.8, 26.7 (d, $^{3}J_{P\text{–}C}$ = 14.9 Hz), 23.3 (d, $^{3}J_{P\text{–}C}$ = 17 Hz), 22.6 (d, $^{2}J_{P\text{–}C}$ = 3.9 Hz), 20.4 (d, $^{2}J_{P\text{–}C}$ = 3.8 Hz), 17.5 (d, $^{1}J_{P\text{–}C}$ = 46.1 Hz), 17.3 (d, $^{1}J_{P\text{–}C}$ = 47.7 Hz), 13.2, 10.9. FTIR (CsI pellet; cm^{-1}(ranked intensity)): 227(21), 248(19), 280(26), 304(25), 440(24), 639(9), 722(20), 807(12), 917(17), 959(14), 1043(6), 1100(8), 1209(2), 1227(18), 1266(7), 1308(13), 1339(5), 1378(10), 1459(3), 1560(11), 1582(1), 1629(16), 1648(27), 2872(15), 2934(23), 3446(22). MS (ESI) $m/z^{+/-}$ (%): 562.1 (55) [monomer], 1124^{2} [dimer]. Anal. calcd. (found): C: 46.79 (48.21), H: 6.92 (7.37).

Preparation of 4-methoxy-biphenyl via Suzuki–Miyaura cross-coupling reaction

A 5 mol% mixture of the catalyst **8** (0.025 g, 0.019 mmol) in trihexyltetradecylphosphonium chloride (0.700 g, 1.348 mmol) was dissolved in CH_2Cl_2 (1.5 mL) to facilitate the transfer of the mixture to a small, narrow Schlenk tube. The bulk of the solvent was removed in vacuo at room temperature, and the remaining residual solvent was removed at 70 °C. The mixture was cooled to room temperature, and neat K_3PO_4 (0.275 g, 1.294 mmol), *p*-methoxyphenyl boronic acid (0.066 g, 0.431 mmol), and iodobenzene (0.080 g, 0.392 mmol) were added followed by the addition of toluene (0.1 mL) and distilled and N_2-purged H_2O (0.2 mL). The reaction mixture was stirred and heated at 70 °C for 5 h, and then the volatile solvents were removed in vacuo at room temperature. A cold finger was fitted to the Schlenk tube and the product was isolated from the ionic liquid mixture by sublimation at 80 °C for 14 h, yielding 4-methoxy-biphenyl as a white solid (0.057 g, 0.309 mmol, 99%). ^{1}H NMR (400.09 MHz, $CDCl_3$) δ (ppm): 7.56 (m, 4H), 7.42 (t, 2H, ^{3}J = 7.6 Hz), 7.30 (t, 1H, ^{3}J = 7.6 Hz), 6.98 (d, 2H, ^{3}J = 8.8 Hz), 3.86 (3, 3H).

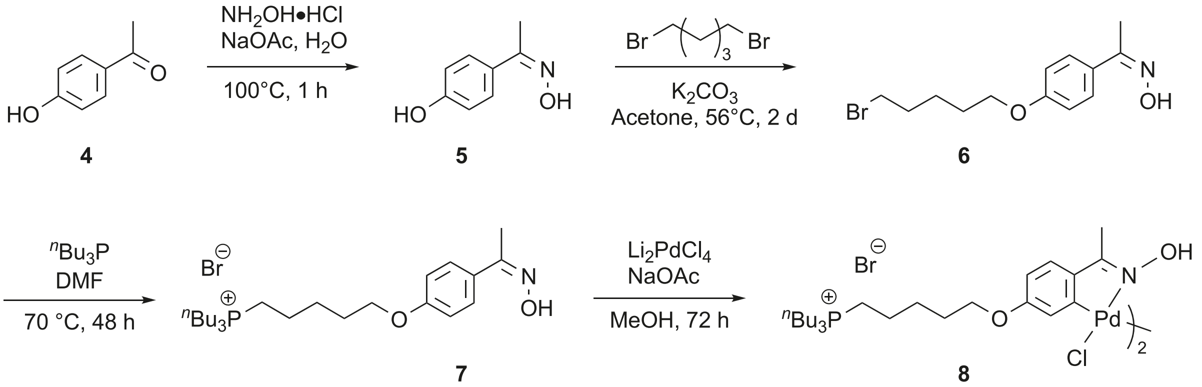
Preparation of trans-stilbene via Heck cross-coupling reaction

A 2 mol% mixture of the catalyst **8** (0.015 g, 0.012 mmol) in trihexyltetradecylphosphonium chloride (0.300 g, 0.578 mmol) was dissolved in CH_2Cl_2 (1.5 mL) to more easily facilitate the transfer of the mixture to a small, narrow Schlenk tube and to assist in the dispersion and solvation of **8** in the ionic liquid solvent. The bulk of the solvent was removed in vacuo at room temperature, and the remaining residual solvent was removed at 70 °C. The mixture was cooled to room temperature, and neat styrene (0.094 g, 0.900 mmol), iodobenzene (0.122 g, 0.600 mmol), and K_3PO_4 (0.255 g, 1.200 mmol) were added, followed by the addition of toluene (0.1 mL) and distilled, N_2-purged, H_2O (0.2 mL). The reaction mixture was stirred and heated at 90 °C for 5 h, and then the volatile solvents were removed in vacuo at room temperature. A cold finger was fitted to the Schlenk tube and the product was isolated from the ionic liquid mixture by sublimation at 80 °C for 14 h, yielding 4-methoxy-biphenyl as a white solid (0.106 g, 0.588 mmol, 98%). ^{1}H NMR (400.09 MHz, $CDCl_3$) δ (ppm): 7.52 (d, 4H, ^{3}J = 8.4 Hz), 7.36 (t, 4H, ^{3}J = 7.6 Hz), 7.26 (t, 2H, ^{3}J = 7.6 Hz), 7.12 (s, 2H).

Procedure for recycling the catalyst and the ionic liquid

Upon completion of the catalysis, the product was isolated following the same procedure as noted. Proton NMR spec-

Scheme 1. Synthesis of phosphonium-functionalized oxime carbopalladacycle **8**.



troscopy of the resulting IL mixture confirmed the complete removal of the product. The reagents were then added in the same amounts, following the initial reaction conditions, and the catalysis was repeated.

Results and discussion

Synthesis

The synthetic route towards the preparation of the phosphonium salt catalyst **8** is summarized in Scheme 1. Compounds **4** through **6** were prepared according to literature procedures.[19] Given the likely reactivity of ^{n}Bu$_3$P with palladium, the generation of the phosphonium salt **7** was completed first, followed by formation of the carbopalladacycle phosphonium salt **8**. The quaternization of tri-*n*-butylphosphine with **6** was monitored by ^{31}P{^{1}H} NMR spectroscopy until the full consumption of ^{n}Bu$_3$P (δ = –32 ppm) was observed.[28] The complete formation of the phosphonium salt (δ = 35 ppm) was detected within 48 h at 70 °C. The DMF was removed in vacuo, and the product was purified by extractions with hexanes and THF, respectively. Comprehensive characterization ascertained the formation of the phosphonium ionic liquid **7** as a yellow, clear, viscous liquid. Thermal analysis of **7** revealed a glass transition temperature of –2 °C and a thermal decomposition temperature of 343 °C. The addition of **7** and NaOAc to methanolic Li_2PdCl_4 resulted in immediate precipitation of a red-brown solid. Upon stirring for 3 days, a beige precipitate also formed. The solids were isolated and washed with MeOH followed by acetone and were finally recrystallized in acetone. The beige powder was fully characterized to confirm the formation of the carbopalladacycle using the following analytical and spectroscopic methods: 1D and 2D NMR spectroscopy, FTIR spectroscopy, UV–vis spectroscopy, electrospray ionization mass spectrometry, differential scanning calorimetry, thermogravimetric analysis, and elemental analysis. The most salient feature in the ^{1}H NMR spectrum was the change in the pattern of the aromatic protons from AA′BB′ to ABC, which was indicative of the formation of the aryl carbopalladacycle environment (Fig. 1).[19,29] The phosphonium carbopalladacycle **8** was isolated as a white powder in a modest yield (19%). Compound **8** was soluble in DCM, DMSO, acetone, and trihexyltetradecylphosphonium chloride, [P_{66614}][Cl], and was insoluble in $CHCl_3$ and apolar solvents, such as alkanes and ethers.

The FTIR spectrum for **7** displayed a characteristic C=N stretching vibration of 1673 cm^{-1}, and the corresponding C=N vibration in **8** was shifted by 26 cm^{-1} (observed at 1648 cm^{-1}), which suggested N–Pd coordination (Fig. 2).[30] Analysis by UV–vis spectroscopy provided further evidence of the presence of the carbopalladacycle in **8**. An absorption at λ_{max} 262 nm and an absorption band at λ_{max} 307 nm with a broad shoulder peak corresponded to ligand centered absorptions on the phosphonium salt. Ionic liquid **7** displayed only one absorption band at λ_{max} 260 nm. The absorption band at λ_{max} 307 nm symbolized charge-transfer transitions, which were specific to metal–ligand orbital interactions, and was in accordance with literature results (Fig. 3).[19]

A typical oxime carbopalladacycle is often a chloro-bridged dimer, which occurs to fulfill the favorable four-coordinate geometry about the palladium centre. However, the imidazolium-tagged oxime carbopalladacycle was found to be monomeric. The last coordination site was filled by the imidazolium, preventing the formation of a dimer.[19] Evidence for both the monomer and dimer phosphonium analogues, **8**, were observed in ESI-MS with the most intense peak attributed to the monomer. The dimer was the most likely conformation, since there was no donor capability at the phosphonium centre in contrast to the imidazolium example. Attempts to grow crystals of suitable quality for X-ray diffraction studies resulted in microcrystalline powders or clusters; thus, solid-state characterization was not possible. No conclusive statement could be made from these results to declare the coordination environment about the palladium.

Catalysis studies

To examine the catalytic ability of the phosphonium carbopalladacycle, two C–C bond forming cross-coupling reactions, Heck and Suzuki–Miyaura, were carried out. The evaluation of the Heck reaction was accomplished using styrene and iodobenzene with K_3PO_4 and, the Suzuki-type reaction was carried out using *p*-methoxyphenylboronic acid and iodobenzene with K_3PO_4 as the base. The reaction conditions including solvents, bases, reaction times, temperature, catalyst loading, and isolation techniques were varied, and the results are summarized in Table 1.

Oxygen-free conditions were required, as reactions carried out in the absence of an inert atmosphere resulted in low yields (Table 1, entries 1, 2, and 14). It was observed that a small amount of toluene and water were required to assist the dissolution of the reagents in the ionic liquid medium,

Fig. 1. Stacked ^{1}H NMR spectra for **7** (bottom) and **8** (top), which clearly display the change in the environment about the phenyl protons, indicative of the incorporation of the palladium metal.

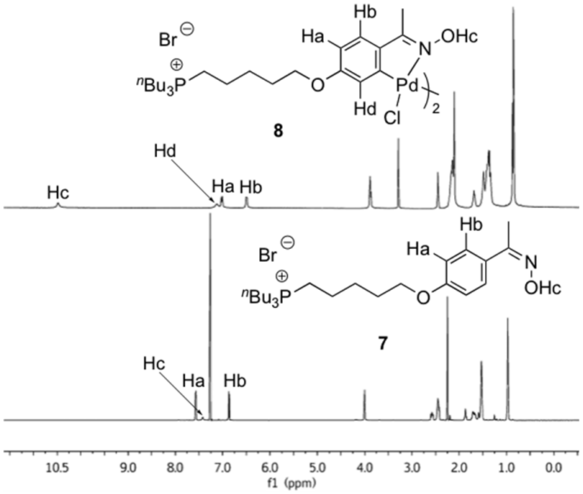
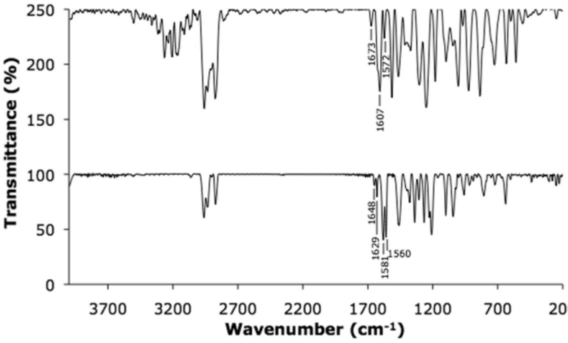


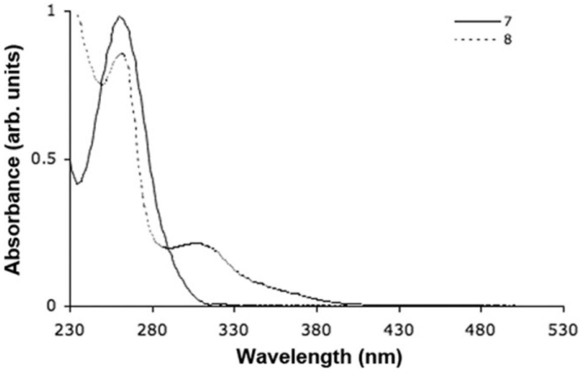
Fig. 2. FTIR spectrum of **7** (top) displays a C=N vibration at 1673 cm^{-1}, and the FTIR spectrum of **8** (bottom) shows the shift of the C=N vibration to 1648 cm^{-1} revealing N–Pd coordination.



as the reaction performed using solely [P$_{66614}$][Cl] yielded only trace amounts of the desired product (Table 1, entry 14). To attain a minimal reaction time under mild temperatures, the ideal catalyst loading was found to be 5 mol% (Table 1, entry 13) for the Suzuki reaction and 2 mol% for the Heck reaction (Table 1, entry 19).

With the use of viscous, non-volatile ionic liquids as solvents in chemical transformations, modifications to the conventional approaches to synthesis and product isolation are necessary. Previously reported product isolation techniques for Suzuki reactions performed in phosphonium ionic liquids were assessed, including aqueous and organic solvent extractions, followed by filtration through silica (Table 1, entries 2, 15, and 16) or alternatively, direct filtration of the reaction mixture through a silica plug (Table 1, entries 1 and 14); all of which proved unsatisfactory for various reasons. Separation of the product by extraction into organic solvent increased volatile solvent use, which is to be avoided if possible. Subsequent filtration through silica increased the steps required to obtain a pure product, which can reduce the final yield. The filtration of the ionic liquid mixture was formerly deemed necessary, since extracting the reaction mixture with hexanes does not always completely remove all of the biaryl product, given some of the biaryl species remains in the ionic liquid phase.[22] This filtration strategy is limited by the inability to reuse the catalyst and solvent because the phosphonium salts predominantly remain coordinated to the silica. However, it is important to note, that herein, no evidence of the phosphonium catalyst **8** was present in the hexanes extractions.

Fig. 3. UV–vis spectra of **7** (solid line) and **8** (dotted line). The emergence of a second band for **8** is indicative of a metal–ligand interaction.



In this context, it was ascertained that the best way to isolate the products was through sublimation. One can take advantage of the non-volatility of the reaction medium and catalyst and simply remove the volatile product by sublimation. Initial experiments were carried out in a small vial (15 × 48 mm) with a septum cap for the delivery of $N_{2(g)}$ by a needle, given the volume of the reaction mixture was small. Upon completion of the reaction, the mixture was dissolved in CH_2Cl_2 and transferred to a Schlenk flask. The volatile solvent was removed under reduced pressure, the flask was then fitted with a cold finger, and the product was sublimed at 0.5 mm Hg and 80 °C. To further optimize the isolation procedure, an unconventionally shaped Schlenk tube was designed not only to accommodate the small reaction volume, but also to include the capacity to fit a cold finger to the flask (Fig. 4). Under the optimized reaction conditions and with the appropriate glassware, high-yielding Suzuki and Heck cross-coupling reactions were achieved (Table 1, entries 13 and 19).

Catalyst recyclability studies

While employing the optimized conditions, the recyclability of the ionophilic catalyst was demonstrated. For both the Heck and Suzuki reactions, upon completion of the reactions, the residual toluene and water were removed in vacuo at room temperature, and subsequently, a cold finger was inserted into the flask and the product was sublimed at 0.5 mm Hg at 80 °C overnight. ^{1}H NMR spectroscopy of the remaining IL mixture confirmed the absence of any product or starting reagents. If residual product was observed in the IL, then a second sublimation was performed. Without removal of any residual borates or phosphates, the starting reagents, not including fresh catalyst, were again added to the ionic liquid mixture and the catalysis was repeated at the optimized conditions, and the results are summarized in Table 2.

Table 1. Reaction conditions studies for the Suzuki- and Heck-type cross-coupling.

Entry	Reaction	*T* (°C)	Time (h)	Catalyst **8** (mol%)	Yield (%)
1	Suzuki[a]	55	1	1	Trace[c,d]
2		70	16	1	29[c,e]
3		70	16	1	76[f]
4		70	16	1	18[g]
5		70	2	1	42[g]
6		70	4	1	76[g]
7		70	6	1	82[g]
8		70	8	1	88[g]
9		70	4	5	83[h]
10		80	7	1	78[h]
12		95	4	1	66[h]
13		70	5	5	98[j]
14	Heck[b]	130	24	2	Trace[c,d,i]
15		90	16	2	75[e]
16		90	16	2	Trace[e]
17		90	4.5	2	73[h]
18		90	6.5	2	74[h]
19		90	5	2	98[j]

[a] Iodobenzene (1 equiv.), *p*-methoxyphenylboronic acid (1.1 equiv.), K_3PO_4 (3.3 equiv.), 0.7 g $[P_{66614}][Cl]$, 0.2 mL H_2O, and 0.1 mL toluene.

[b] Iodobenzene (1 equiv.), styrene (1.5 equiv.), K_3PO_4 (2 equiv.), 0.3 g $[P_{66614}][Cl]$, 0.2 mL H_2O, and 0.1 mL toluene.

[c] Under atmospheric conditions.

[d] Product isolation by silica column filter.

[e] Product isolation by extraction with hexanes followed by silica column filter.

[f] Product isolation by extraction with hexanes, removal of solvent under reduced pressure followed by sublimation.

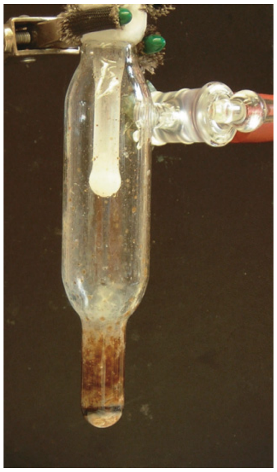
[g] Product isolation by aqueous extraction and sublimation of the remaining reaction mixture.

[h] Product isolation by sublimation from reaction mixture.

[i] No toluene or water added; NaOAc as base.

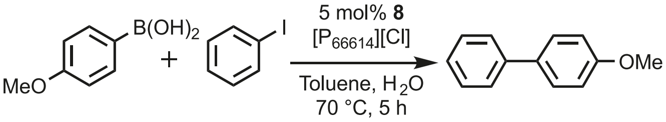
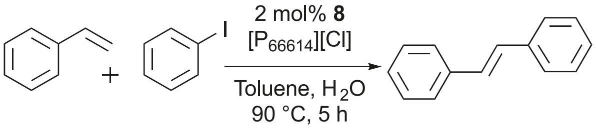
[j] Product isolation by sublimation in reaction flask.

Fig. 4. Sublimation of *trans*-stilbene from the ionophilic catalyst **8** – $[P_{66614}][Cl]$ reaction mixture using the specially designed reaction tube.



The ionophilic catalyst **8** – $[P_{66614}][Cl]$ mixture was recycled three times before any decrease in activity was observed for the Suzuki reaction. After the third reuse of the catalyst, the IL mixture changed from yellow to black. This is likely due to the formation of Pd black and is probably associated with the decrease in conversion. The phosphonium catalyst **8** exhibited good catalytic activity in Heck reaction as well; however, the recyclability of the catalyst was poor. The yields decreased by 20% on the second cycle and continued to diminish rapidly over the subsequent cycles. Again, the colour of the reaction mixture changed from yellow to a red-black on the first cycle, indicative of the initiation of catalyst decomposition. However, it is important to note that while **8** exhibits moderate recyclability, the imidazolium carbopalladacycle ionophilic catalyst by Corma et al. displayed quite low reactivity. The Heck and Suzuki coupling reactions exhibited yields ranging from 3%–25% on the first run, and therefore, the catalyst was not recyclable.[19] They proposed that the imidazolium tag was unstable under the basic conditions required, and the formation of carbene by deprotonation at C-2 on the imidazolium prevailed. The resulting carbene would then coordinate to the palladium and ultimately result in the decomposition of the catalyst, the formation of Pd black, and poor catalytic activity. Therefore, the substitution of a phosphonium salt for an imidazolium cation proves to be a more effective route towards the generation of an ionophilic tag for oxime carbopalladacycle cross-coupling reaction catalysts, given basic conditions are required for these types of reactions.

Table 2. Recyclability of **8** in Suzuki and Heck cross-coupling reactions.

Reaction	Cycle	Isolated yield (%)
Suzuki		
	1	92
	2	95
	3	99
	4	93
	5	66
Heck		
	1	87
	2	67
	3	37
	4	18
	5	—

Conclusions

A phosphonium-tagged oxime carbopalladacycle catalyst **8** has been synthesized and comprehensively characterized. The catalyst displayed ionophilic properties in the C–C bond forming cross-coupling Heck and Suzuki reactions conducted in an ionic liquid medium. Based on the ionic nature of **8**, the catalyst selectively partitioned into the ionic liquid reaction phase, and furthermore, the ionic catalyst – solvent media allowed the isolation of the reaction products simply by sublimation without the need to use volatile organic solvents for extraction/separation techniques. This straightforward product-isolation methodology enabled and simplified the recycling of the catalyst and the reaction solvent. The substitution of a phosphonium appendage on an oxime carbopalladacycle as opposed to an imidazolium functionality resulted in increased tolerance towards the basic conditions required in Heck and Suzuki reactions and therefore increased catalytic activity.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), the Ontario Ministry of Research and Innovation, and The University of Western Ontario for funding. We also thank Professor K. M. Baines for the use of TGA and DSC instrumentation, D. Hairsine for the acquisition of mass spectrometry data, and Y. Rambour for glassware fabrication.

References

(1) Rogers, R. D.; Seddon, K. R. *Ionic Liquids as Green Solvents: Progress and Prospects;* American Chemical Society: WA, 2003.
(2) Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107* (6), 2183. doi:10.1021/cr050942s. PMID:17564479.
(3) Welton, T. *Green Chem.* **2008**, *10* (5), 483. doi:10.1039/b805586f.
(4) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis,* 2nd ed.; WILEY-VCH: Weinheim, 2008; Vol. 1.
(5) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107* (6), 2615. doi:10.1021/cr050948h. PMID:17518502.
(6) Welton, T. *Coord. Chem. Rev.* **2004**, *248* (21-24), 2459. doi:10.1016/j.ccr.2004.04.015.
(7) Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett.* **2001**, *3* (23), 3785. doi:10.1021/ol016769d. PMID: 11700138.
(8) Wang, R.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2006**, *71* (1), 426. doi:10.1021/jo052098b. PMID:16388677.
(9) Wang, B.; Zeng, Z.; Twamley, B.; Piekarski, M.; Shreeve, J. M. *Eur. J. Org. Chem.* **2007**, *2007* (4), 655. doi:10.1002/ejoc.200600828.
(10) Šebesta, R.; Kmentová, I.; Toma, Š. *Green Chem.* **2008**, *10* (5), 484. doi:10.1039/b801456f.
(11) Lin, I. J. B.; Vasam, C. S. *J. Organomet. Chem.* **2005**, *690* (15), 3498. doi:10.1016/j.jorganchem.2005.03.007.
(12) Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126* (48), 15876. doi:10.1021/ja0463482. PMID:15571412.
(13) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64* (14), 3047. doi:10.1016/j.tet.2007.12.036.
(14) Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun. (Camb.)* **2002**, (15): 1612. doi:10.1039/b203079a. PMID: 12170807.
(15) Magna, L.; Chauvin, Y.; Niccolai, G. P.; Basset, J.-M. *Organometallics* **2003**, *22* (22), 4418. doi:10.1021/om021057s.
(16) Mathews, C. J.; Smith, P. J.; Welton, T. *J. Mol. Catal. Chem.* **2004**, *214* (1), 27. doi:10.1016/j.molcata.2003.11.030.
(17) Wang, R.; Xiao, J. C.; Twamley, B.; Shreeve, J. M. *Org. Biomol. Chem.* **2007**, *5* (4), 671. doi:10.1039/b616529j. PMID:17285176.
(18) Wan, Q.-X.; Liu, Y.; Cai, Y.-Q. *Catal. Lett.* **2009**, *127* (3-4), 386. doi:10.1007/s10562-008-9700-5.
(19) Corma, A.; García, H.; Leyva, A. *Tetrahedron* **2004**, *60* (38), 8553. doi:10.1016/j.tet.2004.06.121.
(20) Alacid, E.; Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Chem. Rec.* **2006**, *6* (3), 117. doi:10.1002/tcr.20077. PMID:16795006.
(21) Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Synthesis* **2004**, (10), 1713.
(22) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. J. *Chem. Commun. (Camb.)* **2002**, (17): 1986. doi:10.1039/b204699g. PMID:12271707.
(23) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, *1996* (11), 1091. doi:10.1055/s-1996-5658.
(24) Gerritsma, D. A.; Robertson, A.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45* (41), 7629. doi:10.1016/j.tetlet.2004.08.103.

(25) Fraser, K. J.; MacFarlane, D. R. *Aust. J. Chem.* **2009**, *62* (4), 309. doi:10.1071/CH08558.

(26) Wong, H.-t.; Pink, C. J.; Ferreira, F. C.; Livingston, A. G. *Green Chem.* **2006**, *8* (4), 373. doi:10.1039/b516778g.

(27) Naik, P. U.; McManus, G. J.; Zaworotko, M. J.; Singer, R. D. *Dalton Trans.* **2008**, (36): 4834. doi:10.1039/b811232k. PMID:18766212.

(28) Kosolapoff, G. M.; Maier, L. *Organic Phosphorus Compounds;* John Wiley & Sons, Inc.: Toronto, ON, 1972; Vol. 2.

(29) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663* (1-2), 46. doi:10.1016/S0022-328X(02)01727-8.

(30) Nielson, A. J. *J. Chem. Soc., Dalton Trans.* **1981**, (1): 205. doi:10.1039/dt9810000205.