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Application of recyclable, polymer-immobilized iodine(III) oxidants in catalytic C–H bond functionalization

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Available online 7 March 2006

Abstract

This paper describes the palladium-catalyzed oxidative functionalization of arene and alkane C–H bonds using the polymer-immobilized iodine(III) oxidant poly-4-(diacetoxyiodo)styrene (PS–I(OAc)$_2$) and its derivatives. These transformations have been applied to a wide range of organic substrates, and typically proceed with excellent levels of regio- and chemoselectivity as well as with high functional group tolerance. In addition, the polymer-immobilized iodine(I) byproducts of these reactions are readily recovered (by precipitation with methanol), reoxidized (with inexpensive peracetic acid), and reused in multiple catalytic transformations without significant loss of reactivity. Variation of the substituents at the iodine(III) center allows the installation of diverse functionalities, including carbon–oxygen, carbon–chlorine, and carbon–carbon bonds.
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*Keywords:* C–H activation; Oxidation; Palladium; Recyclable; Iodobenzene diacetate

1. Introduction

The development of mild and efficient transition metal-catalyzed methods for the oxidative functionalization of carbon–hydrogen bonds remains an important challenge in organic and organometallic chemistry [1–18]. In particular, C–H activation/functionalization reactions that proceed regioselectively in the context of complex organic substrates could provide important new synthetic approaches to fine chemicals, pharmaceutical intermediates, organic materials, and natural products [10–18]. We have recently reported a Pd(OAc)$_2$-catalyzed method for the selective acetoxylation of arene and alkane C–H bonds using PhI(OAc)$_2$ as a stoichiometric oxidant [9–12]. These transformations proceed under mild conditions ($\leq$100 °C) and with very high (typically >99%) levels of regioselectivity with substrates containing coordinating functional groups (L). As summarized in Scheme 1, these groups (L) serve to bind to the palladium catalyst and direct C–H activation and subsequent oxidation to a specific C–H bond within the molecule [19].

This methodology represents an attractive approach to the selective oxidation of diverse organic molecules on a research laboratory scale; however, the stoichiometric oxidant PhI(OAc)$_2$ remains quite expensive (at approximately $ 1/g [20]) for large-scale applications. Additionally, the atom economy and environmental impact of this method is less than ideal, as one equivalent of toxic iodobenzene is generated with each catalytic turnover and must be separated from the organic product (often requiring inefficient column chromatography). These drawbacks led us to consider the possibility that a recyclable polymer-immobilized derivative of PhI(OAc)$_2$ – poly-4-(diacetoxyiodo)styrene [PS–I(OAc)$_2$] – might be used in these transformations as an environmentally friendly alternative to the monomeric oxidant. Importantly, PS–I(OAc)$_2$ and its derivatives are readily available in two steps from commercial polystyrene [21–27]. Furthermore, this reagent has been widely used in organic synthesis for reactions including the iodination of arenes, the α-hydroxylation of ketones, and the oxidation of sulfides, hydroquinones, phenols, and alcohols [21–27]. PS–I(OAc)$_2$ generally shows comparable (or moderately lower) reactivity to PhI(OAc)$_2$ in these transformations; furthermore, the poly-4-iodostyrene (PS–I) byproduct is readily recovered and recycled, rendering these processes safe and environmentally benign. We report herein the use of PS–I(OAc)$_2$ and its derivatives as stoichiometric oxidants for the Pd(OAc)$_2$-catalyzed ligand-directed oxidation of organic substrates. The reactivity, substrate scope, and functional group tolerance of these processes have been explored in detail and are compared

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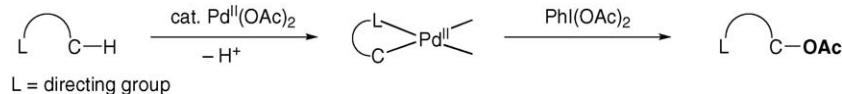
Scheme 1. Pd(OAc)$_2$-catalyzed ligand-directed C–H acetoxylation with PhI(OAc)$_2$.

to those with PhI(OAc)$_2$. In addition, the recovery and reuse of the polymer-immobilized oxidant from these reactions is described.

2. Experimental

Catalytic reactions were conducted under ambient air and moisture in 20 mL vials fitted with Teflon-lined caps. Poly-4-iodostyrene [21], poly-4-(diacetoxyiodo)styrene [21], poly-4-(dichloroiodo)styrene [24], and poly-[4-(phenyliodo)styrene] BF$_4$ [23] were synthesized according to literature procedures or with the modifications described below. The poly-4-(diacetoxyiodo)styrene reproducibly contained 88% active oxidant (as measured by iodometry), and all stoichiometries were calculated based on this value. Substrates **1–3** and **10–13** were purchased from commercial sources (Acros, Lancaster, Aldrich) and used as received. Substrates **4–9** and **14** were synthesized via published procedures [10,11]. Control reactions were run for each substrate (in the absence of Pd catalyst) and generally showed no reaction under our standard conditions.

2.1. Synthesis of poly-4-iodostyrene (PS–I)

Polystyrene (8 g, 76.5 mmol), I$_2$ (9 g, 35.5 mmol), and I$_2$O$_5$ (3.5 g, 10.9 mmol) were dissolved in a mixture of CCl$_4$ (20 mL), 50% aqueous H$_2$SO$_4$ (17 mL), and nitrobenzene (100 mL). Notably, we found it critical to use new bottles (or freshly distilled) CCl$_4$ and nitrobenzene in this reaction to avoid the formation of an intractable oily black product. The reaction mixture was stirred at 90 °C for 40 h, cooled to room temperature, and diluted with 50 mL of chloroform. The light orange product was precipitated by the addition of approximately 700 mL of methanol. The PS–I was purified by three sequential precipitations from chloroform solution with methanol to afford 10.1 g (81% yield) of an off-white solid. Elemental analysis revealed that 88% of the polystyrene phenyl groups were iodinated.

2.2. Synthesis of poly-4-(phenyliodo)styrene tetrafluoroborate [PS–I–Ph]BF$_4$

PS–I(OAc)$_2$ (6 g, 17.1 mmol) and benzene (30 mL) were combined in 100 mL of acetic acid. Concentrated sulfuric acid (30 mL) was added dropwise over 25 min and the resulting solution was stirred at ambient temperature for 60 h. Water (200 mL) was added to the reaction mixture to precipitate a dark yellow solid, which was collected by filtration to afford [PS–I–Ph]HSO$_4$ (4.4 g, 14.1 mmol, 83%). [PS–I–Ph]HSO$_4$ (1.1 g, 3.5 mmol) was then suspended in 30 mL of an aqueous solution of NaBF$_4$ (13.5 g, 13 mmol, 25 equiv.) and stirred for 48 h. The resulting insoluble light brown solid was isolated by filtration and dried under vacuum to afford [PS–I–Ph]BF$_4$ (0.95 g, 3.5 mmol, 99% yield).

### 2.3. General procedure for Pd-catalyzed acetoxylation with PS–I(OAc)$_2$

The organic substrate (1 equiv., 0.05–0.1 M), PS–I(OAc)$_2$ (1.7–2.7 equiv.) and Pd(OAc)$_2$ (5 mol%) were combined in acetic acid or a mixture of acetic acid/acetic anhydride and stirred for 3–12 h at 100 °C. The reaction was cooled to room temperature, and the PS–I was precipitated with methanol, collected on a frit, and washed with methanol. The reaction solution and washings were combined and evaporated to dryness to afford the organic products. In some cases (**1a–3a**) this procedure afforded analytically pure material; however, with the other substrates (which contain multiple possible sites for directed oxidation and/or in which traces of starting material remained) the product was further purified by chromatography on silica gel [10,11].

2.4. General procedure for Pd(OAc)$_2$-catalyzed chlorination with PS–I(Cl)$_2$

Substrate **12** (115 mg, 0.75 mmol, 1 equiv.), PS–I(Cl)$_2$ (680 mg, 2.7 equiv.), and Pd(OAc)$_2$ (8.4 mg, 0.0375 mmol, 5 mol%) were combined in methylene chloride (2 mL) and stirred for 12 h at 100 °C. The reaction was cooled to room temperature, and the PS–I was precipitated with methanol (2 mL), collected on a frit, and washed with methanol (5 mL). The reaction solution and washings were combined and evaporated to dryness to afford a clear oil, which was redissolved in methylene chloride (2 mL). Biphenyl was added to the solution as an internal standard, and the yields of products **12b** (50%) and **12c** (25%) were determined by GC and GCMS analysis.

2.5. General procedure for phenylation with [PS–I–Ph]BF$_4$

Substrate **14** (65 mg, 0.38 mmol, 1 equiv.), [PS–I–Ph]BF$_4$ (300 mg, 1.8 equiv.) and Pd(OAc)$_2$ (5 mg, 0.019 mmol, 5 mol%) were combined in a 4:1 mixture of acetic acid to acetic anhydride (2 mL) and stirred for 12 h at 100 °C. The insoluble oxidant was removed by filtration and was washed with methylene chloride (8 mL). The solvent was then removed, and the resulting oil was redissolved in methylene chloride (30 mL), washed with saturated NaHCO$_3$ (3 × 30 mL^2) and brine (1 × 30 mL^2) and dried with MgSO$_4$. The solvent was removed under vacuum and the resulting oil was purified by chromatography on silica gel according to a published procedure [28] to afford **14a** as a clear oil (66.7 mg, 71% yield).

Trial	Yield 1a	Yield PS–I(OAc)$_2$
1	72%	85%
2	77%	81%
3	82%	84%
4	76%	81%
5	75%	86%
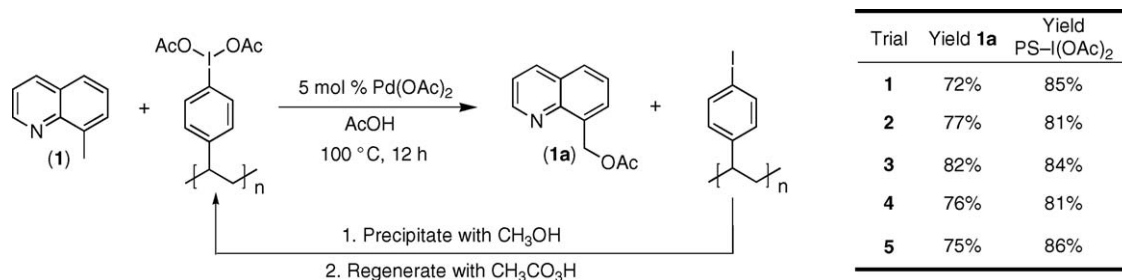
Scheme 2. Oxidant regeneration and reuse in the Pd-catalyzed acetoxylation of **1**.

3. Results and discussion

Our initial studies focused on the Pd(OAc)$_2$-catalyzed ace-toxylation of 8-methylquinoline (**1**) using PS–I(OAc)$_2$ as the stoichiometric oxidant. As shown in Scheme 2, the reaction of **1** with 1.7 equiv. PS–I(OAc)$_2$ and 5 mol% Pd(OAc)$_2$ at 100 °C for 12 h afforded the acetoxylated product **1a** in 77% isolated yield. Conveniently, this reaction did not require special handling/purification of the solvents or reagents, and was carried out in commercial acetic acid in the presence of ambient air and moisture. The yield obtained using the polymer-immobilized oxidant was slightly lower than with PhI(OAc)$_2$ under comparable conditions (77% versus 88%), and systematic studies revealed that more oxidant (1.7 equiv. PS–I(OAc)$_2$ versus 1.1 equiv. PhI(OAc)$_2$) was required to drive the reactions to completion [29]. This may be due to the moderate solubility of PS–I(OAc)$_2$ in acetic acid and/or the decreased accessibility of the immobilized oxidant to the active palladium catalyst [29]. Notably, Togo et al. reported similarly reduced reactivity of PS–I(OAc)$_2$ relative to PhI(OAc)$_2$ in arene iodination reactions and in the 1,2 aryl migration of alkyl aryl ketones [21].

A significant advantage of reactions with PS–I(OAc)$_2$ is that column chromatography is not required to separate PS–I from the oxidized organic product. Instead, PS–I can be removed by simple precipitation with methanol, providing **1a** in high yield and purity. This procedure also facilitates recycling of the PS–I, which can be reoxidized with peracetic acid [21] to recover PS–I(OAc)$_2$ from the catalytic reactions in 80–85% yield (determined based on the mass of the recovered polymeric oxidant). As summarized in Scheme 2, the sequence of Pd(OAc)$_2$-catalyzed acetoxylation of **1** with PS–I(OAc)$_2$ followed by recovery and recycling of PS–I with CH$_3$CO$_3$H could be repeated five times with comparable yields of **1a** and recovered PS–I(OAc)$_2$ for each run. Importantly, these results reveal no loss in activity of the regenerated oxidant over the course of five rounds of recycling.

We next examined the substrate scope of Pd(OAc)$_2$-catalyzed directed sp^3-C–H bond acetoxylation using PS–I(OAc)$_2$ as the stoichiometric oxidant. As summarized in Table 1, a wide variety of alkane substrates containing both pyridine (**1–3**) and oxime (**4–7**) directing groups underwent highly regioselective acetoxylation in good yields. In general, the isolated yields from these reactions were similar (±10%) to those reported with PhI(OAc)$_2$ [11], and the reactivity of PS–I(OAc)$_2$ was comparable to or only slightly lower than that of free PhI(OAc)$_2$ (with 1.7 equiv. of PS–I(OAc)$_2$ versus 1.1–2.0 equiv. of PhI(OAc)$_2$ typically
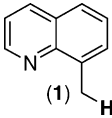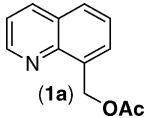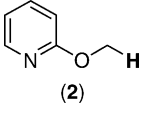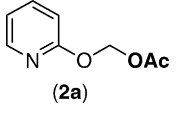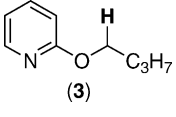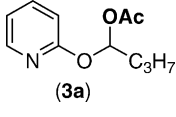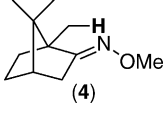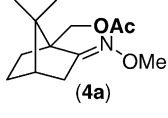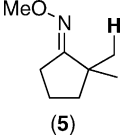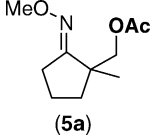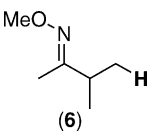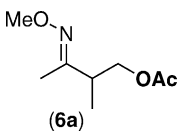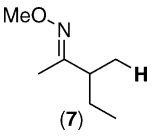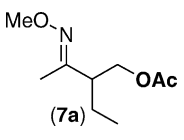
required for complete conversion) [29]. Notably, in keeping with our results with PhI(OAc)$_2$, the oxidation of **7** (which contains six different types of C–H bonds) proceeded to afford **7a** as a single regioisomeric product. This result is consistent with a strong preference for activation of 1° (relative to 2°) sp^3-C–H bonds via 5-membered (rather than 6-membered) palladacyclic intermediates.

Catalytic directed C–H activation/acetoxylation with PS–I(OAc)$_2$ was also applied to the functionalization of sp^2-C–H bonds in a variety of arene substrates. As summarized in Table 2, oxime ethers, pyrazoles, pyridines, and amides all served as effective directing groups for these transformations, and a wide variety of functionalities, including benzylic C–H bonds, enolizable oximes, and aryl bromides were well tolerated. Substrates **8–11** reacted with 5 mol% Pd(OAc)$_2$ and 2.7 equiv. of PS–I(OAc)$_2$ to afford the mono-*ortho*-acetoxylated products **8a–11a** in good to excellent yields (entries 1–4). In substrate **8**, which contains two different *ortho*-C–H bonds, acetoxylation took place exclusively at the less sterically hindered *ortho*-position, consistent with our previous studies with PhI(OAc)$_2$ [12]. Notably, the reactions of substrates **10** and **11** (which proceed via 6-membered palladacycles) with 2.7 equiv. of PS–I(OAc)$_2$ produced mono-functionalized species as the major products. In contrast, under the same conditions, substrates **12** and **13** (which react via 5-membered palladacyclic intermediates) afforded the di-*ortho*-acetoxylated products **12a** and **13a** in high yields. Similar trends are observed in reactions with PhI(OAc)$_2$, and likely reflect the rate of C–H activation as a function of palladacycle size and structure [19].

We next sought to expand the applications of polymer immobilized oxidants to diverse Pd(OAc)$_2$-catalyzed directed C–H activation/functionalization reactions. Previous work has shown that the substitution of PhI(OAc)$_2$ with a different iodine(III) reagent (such as PhI(Cl)$_2$ [30] or [Ar–I–Ar]$^+$ [28,31]) or with an alternative oxidant (such as *N*-bromosuccinimide [10] or I$_2$ [14]) in these transformations results in the formation of carbon–halogen or carbon–carbon bonds in high yields. As summarized in Scheme 3, these reactions are all believed to proceed via similar mechanisms, involving: (i) ligand-directed C–H activation, (ii) oxidation of the resulting Pd^{II} metallacycle to Pd^{IV}, and (iii) C–X bond-forming reductive elimination (X = OAc, Cl, Br, I, Ar) to afford the functionalized product [28,32].

The polystyrene-immobilized chlorinating reagent PS–I(Cl)$_2$ was prepared via reaction of PS–I with Cl$_2$ according to a literature procedure [24], and was found to be an effective oxidant for

Table 1
Substrate scope of chelate-directed sp^3-C–H bond acetoxylation with PS–I(OAc)$_2$[a]

Entry	Substrate	Product	Yield[b]
1	(1)	(1a)	77% (88%)
2	(2)	(2a)	70% (66%)
3	(3)	(3a)	73% (83%)
4	(4)	(4a)	78% (75%)
5	(5)	(5a)	59% (61%)
6	(6)	(6a)	67%[c] (74%)
7	(7)	(7a)	73%[c] (78%)

[a] Conditions: 5 mol% Pd(OAc)$_2$, 1.7 equiv. PS–I(OAc)$_2$, 1 equiv. substrate (0.05 M in AcOH or 50% AcOH/50% Ac$_2$O), 3–12 h, 100 °C.

[b] Isolated yields (reported as an average of two runs). Yields in parentheses are those obtained with monomeric PhI(OAc)$_2$.

[c] Isolated as a mixture of oxime E/Z isomers.

the Pd^{II}-catalyzed *ortho*-chlorination of 2-phenylpyridine (**12**). In the presence of 5 mol% Pd(OAc)$_2$ and 2.7 equiv. PS–I(Cl)$_2$ in CH$_2$Cl$_2$ at 100 °C, **12** underwent reaction to afford a clean mixture of mono-*ortho*-chlorinated product **12b** (50% yield) and di-*ortho*-chlorinated product **12c** (25% yield) (Scheme 4) [29].
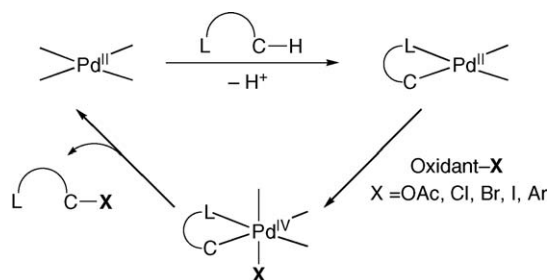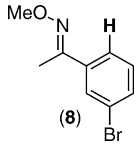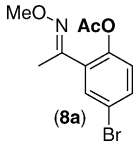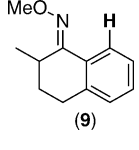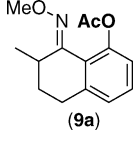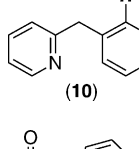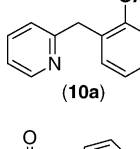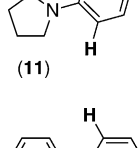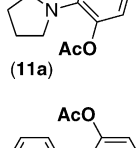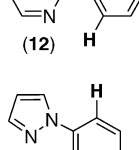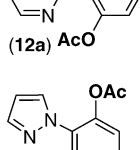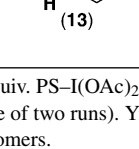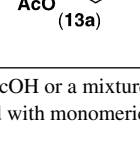

Scheme 3. Proposed catalytic cycle for Pd^{II} C–H activation/functionalization with diverse oxidants.

Once again, the PS–I byproduct could be conveniently recovered by precipitation from the reaction mixture with methanol and regenerated by treatment with Cl$_2$. However, the broad utility of PS–I(Cl)$_2$ in these transformations was limited by its low thermal stability [24], as well as by its tendency to promote the uncatalyzed background chlorination of many substrates. (Notably, the monomeric oxidant PhI(Cl)$_2$ suffers from similar limitations [30].) As such, we generally prefer to use more stable *N*-halosuccinimide derivatives as stoichiometric oxidants for Pd(OAc)$_2$-catalyzed directed halogenation reactions [10,30].

The polymer tethered bis-aryliodonium reagent [PS–I–Ph]BF$_4$ was prepared by stirring PS–I(OAc)$_2$ in a mixture of benzene, acetic acid, and sulfuric acid [23] followed by anion exchange with NaBF$_4$. [PS–I–Ph]BF$_4$ (1.8 equiv.) reacted with 2-phenyl-3-methylpyridine (**14**) in the presence of 5 mol% Pd(OAc)$_2$ to afford the *ortho*-phenylated product **14a** in 71% isolated yield (Scheme 5). Notably, this yield was reproducibly lower than the 88% yield obtained with

Table 2
Substrate scope of chelate-directed sp^2-C–H bond acetoxylation with PS–I(OAc)$_2$[a]

Entry	Substrate	Product	Yield[b]
1	(8)	(8a)	86%[c] (81%)
2	(9)	(9a)	75%
3	(10)	(10a)	52%[d] (44%)
4	(11)	(11a)	55%[e] (77%)
5	(12)	(12a)	85% (83%)
6	(13)	(13a)	80%

[a] Conditions: 5 mol% Pd(OAc)$_2$, 2.7 equiv. PS–I(OAc)$_2$, 1 equiv. substrate (0.05–0.06 M in AcOH or a mixture of AcOH/Ac$_2$O), 12 h, 100 °C.

[b] Isolated yields (reported as an average of two runs). Yields in parenthesis are those obtained with monomeric PhI(OAc)$_2$ (when available).
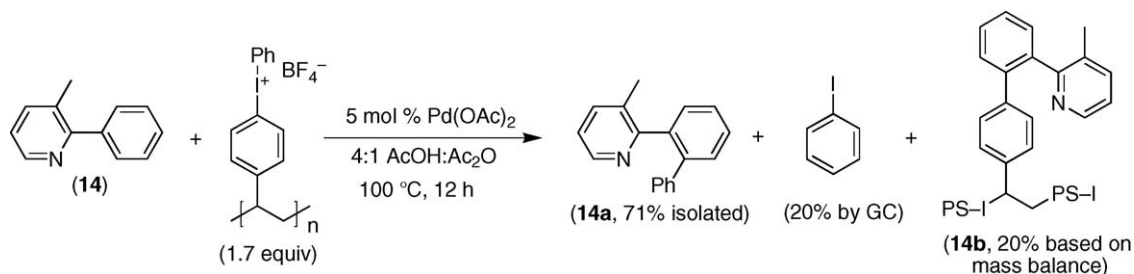
[c] Isolated as a mixture of oxime E/Z isomers.

[d] Unreacted starting material (8%) and the bis-*ortho*-acetoxylated product (25%) observed by GCMS of the crude reaction mixture.

[e] Unreacted starting material (33%) remained by GCMS of the crude reaction mixture.
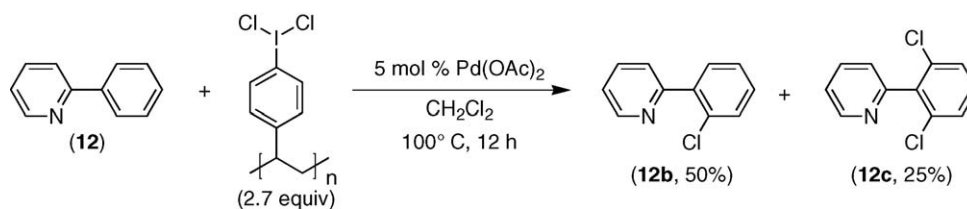
Scheme 4. C–H activation/C–Cl bond formation with PS–I(Cl)$_2$.

Scheme 5. Catalytic C–H activation/C–C bond formation with [PS–I–Ph]BF$_4$.

the monomeric oxidant [Ph–I–Ph]BF$_4$ [28]; furthermore, a significant quantity of iodobenzene ($\sim$20%) was observed by GC in the crude reaction mixture. These results suggest that the two aryl groups undergo competing transfer to the substrate [28], implying the formation of polymer-immobilized C–C coupled product **14b** in approximately 20% yield. While this competing polymer arylation reaction limits the recyclability of the arylating reagent, it represents a potentially useful C–H activation-based methodology for covalent attachment of functionalized organic molecules onto solid supports. Further investigations to characterize **14b** and related materials as well as to increase the yield and expand the scope of these polymer immobilization reactions are ongoing.

4. Conclusions

In conclusion, we have demonstrated the use of polymer-immobilized iodine(III) oxidants in a variety of Pd(OAc)$_2$-catalyzed ligand-directed C–H activation/functionalization reactions. In general, the polymer immobilized oxidants, including PS–I(OAc)$_2$, PS–I(Cl)$_2$, and [PS–I–Ph]BF$_4$, show reactivity and functional group tolerance that is comparable to their soluble monomeric analogues. The PS–I byproduct of these reactions is readily recovered (via precipitation from the reaction mixture with methanol) and regenerated multiple times, rendering these oxidants practical recyclable alternatives to PhI(OAc)$_2$ for Pd-catalyzed C–H activation/functionalization reactions.

Acknowledgements

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