



HandaPhos: A General Ligand Enabling Sustainable ppm Levels of Palladium-Catalyzed Cross-Couplings in Water at Room Temperature

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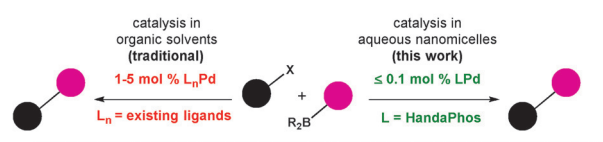
Abstract: The new monophosphine ligand HandaPhos has been identified such that when complexed in a 1:1 ratio with $\text{Pd}(\text{OAc})_2$, enables Pd-catalyzed cross-couplings to be run using ≤ 1000 ppm of this pre-catalyst. Applications to Suzuki–Miyaura reactions involving highly functionalized reaction partners are demonstrated, all run using environmentally benign nanoreactors in water at ambient temperatures. Comparisons with existing state-of-the-art ligands and catalysts are discussed herein.

Ligated palladium remains among the most enthusiastically utilized catalysts in synthetic and materials chemistry.^[1] The Nobel Prize awarded to Heck, Negishi, and Suzuki in 2010 serves to encourage further use and applications of these transition metal-mediated reactions.^[2] Unfortunately, the world's supply of economically accessible palladium is limited; i.e., it is an endangered element.^[3] Hence, aside from its status as a precious and, therefore, costly metal, there is considerable incentive to address this issue from the perspective of sustainability. Perhaps of equal impact, especially for the pharmaceutical industry, is the amount of residual palladium found in the products, which typically requires special processing to reduce to FDA-approved levels. Two options include a move away from palladium entirely, or use of palladium at especially low levels, and preferably, with recycling. While alternative transition metals, such as nickel^[4] and copper,^[5] may be attractive for certain applications, palladium remains the metal of choice. Traditional uses of palladium catalysts under homogeneous conditions in organic solvents tend to employ catalyst loadings in the range of 1–5 mol %. While there are isolated examples in the literature where ppm,^[6] and even ppb,^[6c–e] levels have been reported, none is of sufficient generality and in virtually all cases, forcing conditions are required. Moreover, regardless of the extent of Pd invested per reaction, neither catalyst nor solvent

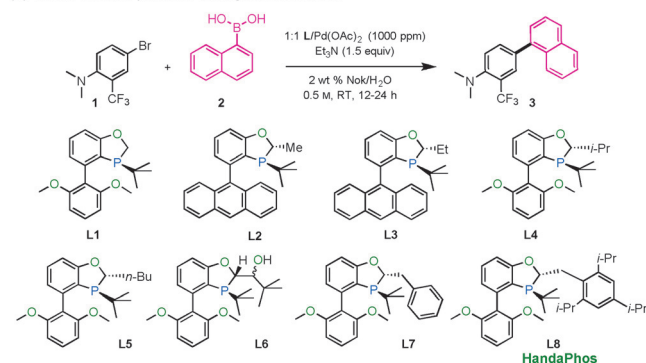
is typically fully recycled, creating considerable organic waste especially at scale.

Here, we disclose a truly general, mild, efficient, and environmentally sustainable technology based on the new ligand, racemic “HandaPhos.” When combined in a 1:1 ratio with $\text{Pd}(\text{OAc})_2$,^[7] a pre-catalyst results that, via in situ reduction, enables Pd-catalyzed Suzuki–Miyaura (SM) cross-couplings to be run in water at room temperature using ppm levels of palladium (Scheme 1 A). In essence, the level of ligated palladium that need be invested can be reduced by 1–2 orders of magnitude. No other technology of this generality and environmental attractiveness applied to couplings of this type is currently known.

(A) sustainable approach to Pd-catalyzed Suzuki–Miyaura cross-couplings



(B) model reaction partners, and ligands examined



Scheme 1. A ligand-based sustainable approach to Pd-catalyzed C–C bond formation.

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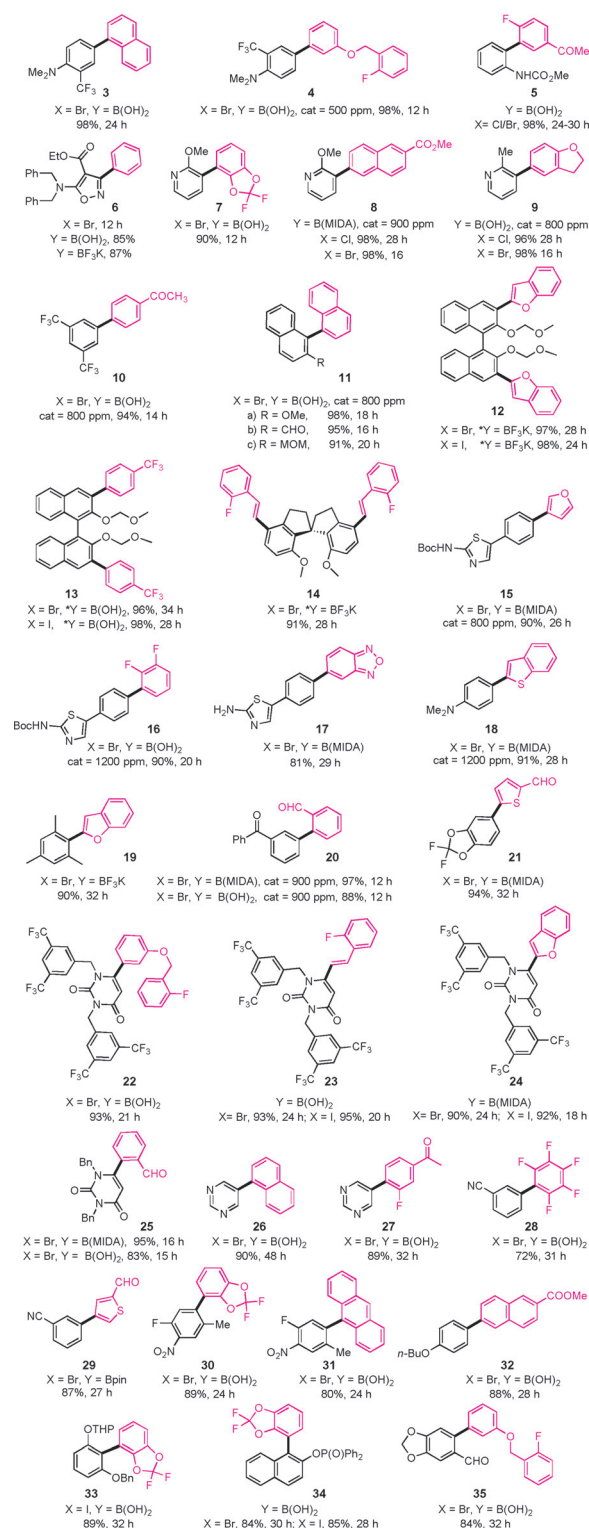
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Traditional Pd-catalyzed sp^2 – sp^2 bond formations carried out in organic solvents rely on ligands cleverly crafted based on crucial steric, conformational, and stereoelectronic properties.^[8] Upon completion, most, if not all, of the active palladium catalyst is either discarded as waste or re-processed in efforts to recover spent precious metal. Rarely is there any attention directed towards recovery/recycling of costly ligands, especially significant at higher catalyst loadings. Indeed, the cost associated with such ligands can oftentimes be more than that for palladium. Moreover, considerable amounts of Pd are usually present within the isolated product, leading to additional metal losses and necessitating further purification.^[9] This latter situation can dictate whether Pd-

catalyzed couplings are even eligible for use at later stages of a synthesis en route to an active pharmaceutical ingredient (API). By contrast, reactions run in size- and shape-controlled nanomicelles feature much higher substrate and catalyst concentrations within their inner cores than those found in organic solvent-based solution. This hydrophobic environment offers a unique opportunity to increase the effective catalyst concentration (i.e., its binding constant) based on its lipophilicity, in addition to adjustments to other standard reaction parameters.^[10] Thus, by increasing the time spent by the catalyst in close proximity to the coupling partners, less catalyst should be needed to achieve coupling within the same or shorter time period.

Our attention was directed towards oxaphosphole-containing ligands in the BI-DIME family, first introduced and extensively studied by Tang et al., and found to be very useful as their derived Pd complexes as catalysts in SM couplings in aqueous toluene using 2–5 mol % of palladium.^[11] Since these catalysts, however, are ineffective under micellar conditions at the 1000 ppm level (0.1 mol %; see below), a structurally related monophosphine with enhanced activity was envisioned based on increased lipophilicity and donicity, while maintaining optimal coordination properties achieved via conformational rigidity, as well as stereoelectronic and steric effects. An extensive investigation of various carbon-based appendages at the 2-position (e.g., **L2–L8**, Scheme 1B) included racemic derivative **L8** bearing a 2,4,6-triisopropylphenylmethyl residue. Remarkably, in a $\approx 1:1$ combination with typically ≤ 1000 ppm of Pd(OAc)₂, this new catalyst efficiently mediates SM cross-couplings at RT. When run in aqueous nanomicelles composed of the inexpensive and commercially available designer surfactant Nok,^[12] along with 1.5–2.0 equivalents of Et₃N, a wealth of functionality in either reaction partner is tolerated. Excellent yields of cross-coupling products are obtained, and no special precautions in catalyst handling are needed insofar as sensitivity towards air and moisture. Moreover, as the extensive survey of products **3–35** illustrates in Scheme 2, this technology is amenable to substrates bearing chloride (e.g., **5**, **8**, and **9**), bromide or iodide as leaving group, although chlorides may require mild heating to 45 °C to reach full conversion. Likewise, the source of boron is especially broad, including boronic acids, Bpin or B(MIDA) derivatives, and BF₃K salts. Noteworthy observations regarding these examples include: a) biaryl products such as **12**, **33**, **34** can be fashioned, notwithstanding their congested state, which might otherwise be very challenging to form in organic solvents at room temperature using even much higher levels of known catalysts; b) alkenylboron derivatives readily participate with equal effectiveness (**14** and **23**).

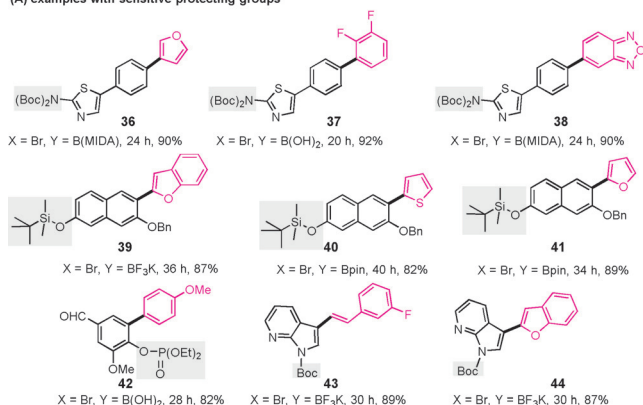
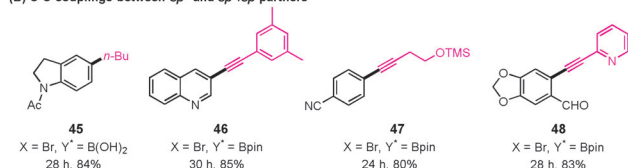
Doubly protected nitrogen, as found in products **36–38** (Scheme 3A), and other sensitive groups, remain intact under these basic albeit especially mild conditions, where ≈ 1000 ppm of (HandaPhos)Pd suffices to afford products **36–44**. Couplings based on other hybridizations at carbon (sp and sp³) are also amenable (Scheme 3B). Attempted coupling using a state-of-the-art catalyst, e.g., (SPhos)palladacycle, under literature conditions (5 mol %, 50 000 ppm)^[13] led predominantly to loss of the Boc protecting group (Sche-



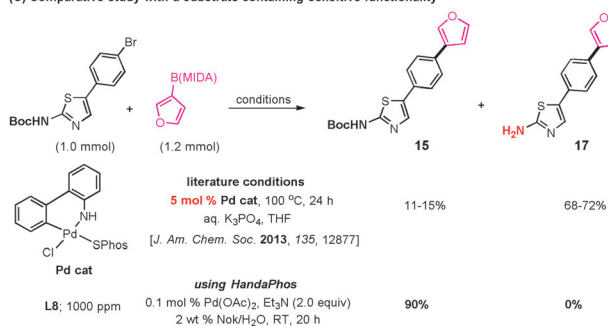
Scheme 2. Representative examples using (HandaPhos)Pd. Unless otherwise mentioned, [Pd] = 1000 ppm (see Supporting Information for details); *Y = added in two equal portions after 12 h at 45 °C. HandPhos: SigmaAldrich catalog number 799580.

me 3C). Similar direct comparisons of Pd ligated by HandaPhos at the 1000 ppm level with other highly acclaimed catalysts clearly documented their limited utility under these

(A) examples with sensitive protecting groups

(B) C-C couplings between *sp*² and *sp*³/*sp* partners

(C) Comparative study with a substrate containing sensitive functionality

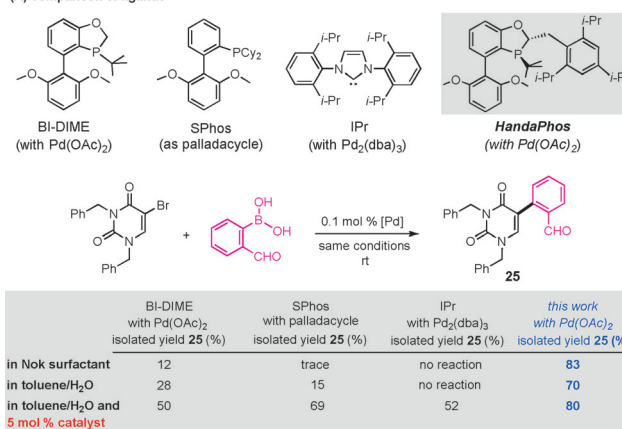


Scheme 3. Substrates with sensitive functionality and/or *sp* and *sp*³ carbon-based reaction partners. Reaction conditions for (A) and (B): 0.5 mmol ArX, 0.53–0.6 mmol Ar'BR₂, 1000 ppm Pd(OAc)₂ 0.01 M in toluene, 1020 ppm HandaPhos, 0.75–1.0 mmol Et₃N, 1.0 mL 2 wt % Nok in H₂O, RT. Unless otherwise mentioned, RT = room temperature. For part (B), reaction temperature is 45 °C. *Y was added in two portions at 12 h intervals (see Supporting Information, pages S17–S18 for a general procedure).

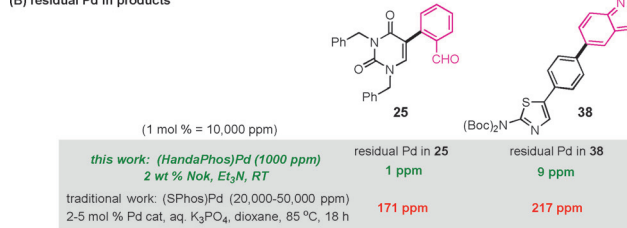
conditions, as little, if any, biaryl product was found in all cases (Scheme 4A). Reactions can be run at global concentrations of 0.5 M or higher; hence, minimal amounts of water are involved. Thus, after in-flask extraction followed by filtration through silica, ICP analysis for Pd content in the product indicated levels on the order of ≤ 9 ppm, which compares very favorably with levels observed using traditional coupling conditions (Scheme 4B).

The amount of Pd invested in each coupling can be reduced further by recycling of the aqueous reaction medium. As described previously in our study of SM using aryl MIDA boronates,^[14] the solid biaryl or related product(s) can be easily obtained by dilution of the reaction mixture with water followed by product isolation via filtration. The filtrate can then be recycled, upon addition of surfactant (back to 2 wt %), and ligated Pd (back to the original ppm level). As summarized in Scheme 4C, couplings between educts **49** and **50** led to consistent isolated yields of biaryl **24** over five cycles.

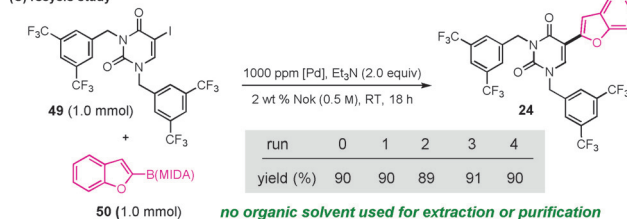
(A) comparison of ligands



(B) residual Pd in products



(C) recycle study

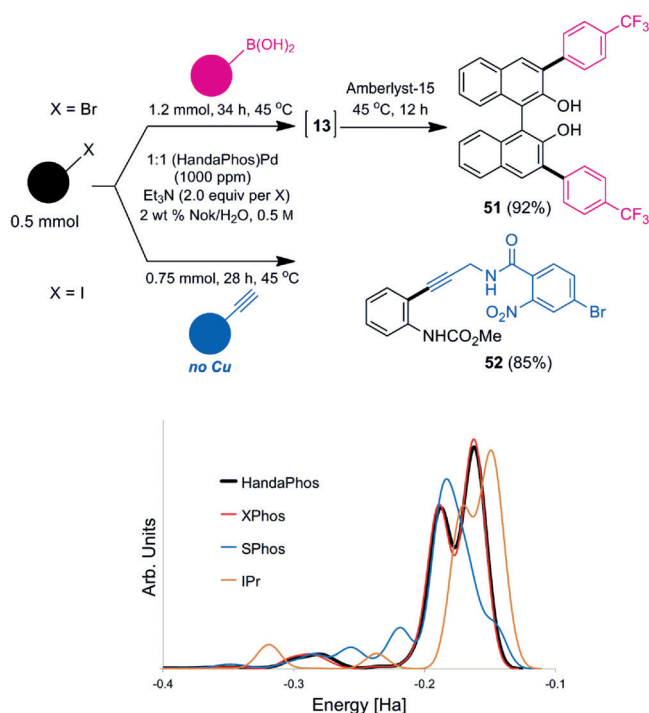


Scheme 4. A) Comparative studies with state-of-the-art ligands; B) levels of Pd in products; C) recycle studies.

Given that organic solvents constitute the vast majority of organic waste created by the chemical enterprise,^[15] in general, an E Factor^[16] calculated based on this reaction variable, therefore, approaches zero; i.e., the reaction from start to finish involves no organic solvent. In addition, all of the water is re-used in subsequent reactions. Future incorporation of HandaPhos into a palladacycle should assist with mechanistic investigations, as well as further reductions in catalyst loadings.

A representative sequence of reactions performed in a single pot is illustrated in Scheme 5 (top). An initial double SM coupling on a bis-MOM-protected 3,3'-dibromo-BINOL is followed by hydrolysis of both MOM residues to afford BINOL **51** in 92% overall yield, highlighting the use of both micellar and the surrounding aqueous media. Prospects for HandaPhos-ligated Pd to mediate analogous Pd-catalyzed Sonogashira couplings, in the absence of copper, were also tested leading to unsymmetrical alkyne **52** (85%), likewise formed in water. Adduct **52** bears several functional groups suggesting that these same mild coupling conditions will allow for considerable scope in the alkyne partner as well.

To gain insight as to the key attributes associated with the design of HandaPhos that impart the observed catalytic



Scheme 5. Top: Tandem reactions to **51**, and Sonogashira coupling to **52**, with ppm levels of (HandaPhos)Pd. Bottom: Occupied density of states (DOS) projected onto the Pd d-orbitals for four mono-ligated Pd catalysts.

activity to its in situ-derived palladium complex, density functional theory (DFT) calculations have been performed using the COSMO-RS implicit solvent model.^[17] This allows for analysis of thermodynamic properties such as solubility, partitioning, interfacial tension,^[18] and reaction free energies in a two-phase system such as exists with Nok-derived nanomicelles in an aqueous medium. Surprisingly, the extent of partitioning of four mono-ligated Pd catalysts containing XPhos, SPhos, IPr, or HandaPhos in this medium is predicted to be virtually identical. Any difference, therefore, ascribed to hydrophobicity of the various ligands should have a minor impact on local concentrations therein, and hence, minimal influence on reaction rates. The electronic structures of these ligands, however, can be quite different (Scheme 5, bottom; also, see Supporting Information). The center of the occupied states projected onto Pd d-orbitals correlates linearly with the reaction energy leading to a stable intermediate from the oxidative addition step. Reaction energy differences span ca. 140 kJ mol⁻¹, implying dissimilarity in resulting catalyst activity as a function of ligand. XPhos and HandaPhos, however, have essentially the same occupied d-orbital center, with only 20 kJ mol⁻¹ between them. Therefore, the potential role of sterics was investigated by calculating the reaction energy in Nok micelles for binding a second ligand of HandaPhos and XPhos to mono-ligated Pd. The free energy of formation between the mono- and di-ligated complexes is +66 kJ mol⁻¹ for HandaPhos, and -62 kJ mol⁻¹ for XPhos. This strongly suggests that HandaPhos forms an exclusively mono-ligated complex with Pd⁰, while XPhos prefers the (less active) di-ligated state. Thus, the

large variations in reactivity, and ultimately, yields, between several established Pd catalysts and HandaPhos(Pd) may be attributed, on the one hand, to the modest role of ligand lipophilicity, while the major influence is due to synergies between steric effects (vs. XPhos) and the electronic structure of HandaPhos (vs. SPhos and IPr).

Overall, this work provides a significant advance in the area of Pd catalysis, and cross-coupling chemistry in particular. Specifically, it offers the synthetic community, based on the new ligand HandaPhos,^[18] the following features now associated with the most heavily utilized of all Pd-catalyzed cross-couplings, the Suzuki–Miyaura reaction, most of which are not characteristic of current methodologies: 1) uses ppm levels of palladium (≤ 0.1 mol %); 2) is generally applicable to a broad range of functionality in either reaction partner; 3) involves very mild conditions, typically room temperature (ca. 22 °C); 4) utilizes an aqueous reaction medium that avoids organic solvents, yet involves very little water—allows for “in-flask” recycling of the surfactant, water, and catalyst; 5) leads to ppm levels of residual palladium in cross-coupling products. The process further illustrates the synthetic potential of micellar catalysis in combination with catalyst design, where enhancing the lipophilic and, in particular, steric and electronic properties of the ligand chelating Pd leads to catalyst loadings that can be reduced to ppm levels. Further applications of HandaPhos-based technology to several other Pd catalyzed reactions (e.g., a more extensive study on Sonogashira couplings), as well as its use with other precious metals (e.g., Au) at the ppm level will be reported in due course.

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- [1] a) Q. Yao, E. P. Kinney, C. Zheng, *Org. Lett.* **2004**, 6, 2997; b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, 348, 609; c) A. DeAngelis, T. J. Colacot in *New Trends in Cross-Coupling: Theory and Applications*, The Royal Society of Chemistry, London, **2015**, pp. 20–90; d) C. C. C. Johansson Seechurn, H. Li, T. J. Colacot in *New Trends in Cross-Coupling: Theory and Applications*, The Royal Society of Chemistry, London, **2015**, pp. 91–138.
- [2] a) T. J. Colacot, *Platinum Met. Rev.* **2011**, 55, 84; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, 51, 5062; *Angew. Chem.* **2012**, 124, 5150; c) G. Molander, J. P. Wolfe, M. Lerhed, *Science of synthesis: cross-coupling and Heck-type reactions*, Workbench

- Edition, Thieme, Stuttgart, **2013**; d) P. G. Gildner, T. J. Colacot, *Organometallics* **2015**, *34*, 5497.
- [3] a) E. Davies, R. Renner, *Chem. World* **2011**, *1*, 50; b) P. Mike, *New Sci.* **2011**, *2*, 2799.
- [4] a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; b) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270; c) S. Handa, E. D. Slack, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2015**, *54*, 11994; *Angew. Chem.* **2015**, *127*, 12162.
- [5] a) M. B. Thathagar, J. Beckers, G. Rothenberg, *J. Am. Chem. Soc.* **2002**, *124*, 11858; b) J. Mao, J. Guo, F. Fang, S.-J. Ji, *Tetrahedron* **2008**, *64*, 3905; c) S. K. Gurung, S. Thapa, A. Kafle, D. A. Dickie, R. Giri, *Org. Lett.* **2014**, *16*, 1264–1267.
- [6] a) R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados, R. D. Singer, *J. Org. Chem.* **2005**, *70*, 161; b) N. E. Leadbeater, V. A. Williams, T. M. Barnard, M. J. Collins, *Org. Process Res. Dev.* **2006**, *10*, 833; c) S. M. Wong, C. M. So, K. H. Chung, C. P. Lau, F. Y. Kwong, *Eur. J. Org. Chem.* **2012**, 4172; d) Z. Dong, Z. Ye, *Adv. Synth. Catal.* **2014**, *356*, 3401; e) C. Deraedt, L. Salmon, D. Astruc, *Adv. Synth. Catal.* **2014**, *356*, 2525.
- [7] In very recent work by Colacot and co-workers, Pd(OAc)₂ has been shown to be more accurately viewed as Pd₃(OAc)₆; see W. A. Carole, J. Bradley, M. Sarwar, T. J. Colacot, *Org. Lett.* **2015**, *17*, 5472.
- [8] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461; c) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916; d) D. Zhang, Q. Wang, *Coord. Chem. Rev.* **2015**, *286*, 1.
- [9] K. Koide in *New Trends in Cross-Couplings: Theory and Applications* (Ed.: T. Colacot), *RCS Catalysis Series*, **2014**, pp. 779–810.
- [10] a) T. Dwars, E. Paetzold, G. Oehme, *Angew. Chem. Int. Ed.* **2005**, *44*, 7174; *Angew. Chem.* **2005**, *117*, 7338; b) S. Handa, D. J. Lippincott, D. H. Aue, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 10658; *Angew. Chem.* **2014**, *126*, 10834; c) G. La Sorella, G. Strukul, A. Scarso, *Green Chem.* **2015**, *17*, 644.
- [11] Q. Zhao, C. Li, C. H. Senanayake, W. Tang, *Chem. Eur. J.* **2013**, *19*, 2261. See also: W. Tang, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, D. Krishnamurthy, N. K. Yee, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2010**, *49*, 5879; *Angew. Chem.* **2010**, *122*, 6015; W. Tang, N. D. Patel, G. Xu, X. Xu, J. Savoie, S. Ma, M. Hao, S. Keshipeddy, A. G. Capacci, X. Wei, Y. Zhang, J. J. Gao, W. Li, S. Rodriguez, B. Z. Lu, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2012**, *14*, 2258; G. Xu, W. Fu, G. Liu, C. H. Senanayake, W. Tang, *J. Am. Chem. Soc.* **2014**, *136*, 570.
- [12] P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888.
- [13] M. A. Dufert, K. L. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 12877.
- [14] N. A. Isley, F. Gallou, B. H. Lipshutz, *J. Am. Chem. Soc.* **2013**, *135*, 17707.
- [15] R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437.
- [16] a) F. Roschangar, R. A. Sheldon, C. Senanayake, *Green Chem.* **2015**, *17*, 752; b) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273; c) B. H. Lipshutz, N. A. Isley, J. C. Fennwald, E. D. Slack, *Angew. Chem. Int. Ed.* **2013**, *52*, 10952; *Angew. Chem.* **2013**, *125*, 11156.
- [17] A. Klamt, F. Eckert, W. Arlt, *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 101.
- [18] M. P. Andersson, M. Bennetzen, A. Klamt, S. L. S. Stipp, *J. Chem. Theory Comput.* **2014**, *10*, 3401.
- [19] HandaPhos will soon be an item of commerce, offered by Sigma–Aldrich (catalog #799580).

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