Tetrahedron Letters 53 (2012) 3990–3993

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# One-step synthesis of reusable, polymer-supported tri-alkyl phosphine ligands. Application in Suzuki–Miyaura and alkoxycarbonylation reactions

Ehsan Ullah [a], James McNulty [a,*], Marcin Sliwinski [a], Al Robertson [b,*]

[a] Department of Chemistry and Chemical Biology, McMaster University, 1280 Main Street West, Hamilton, Canada L8S 4M1
[b] Cytec Canada, Inc., PO Box 240, Niagara Falls, Ontario, Canada L2E 6T4

ARTICLE INFO

*Article history:*
Received 19 April 2012
Accepted 19 May 2012
Available online 28 May 2012

*Keywords:*
Catalyst design
Catalyst recycling
Suzuki–Miyaura reaction
Palladium
Carbonylation

ABSTRACT

A simple, efficient one-step route to polystyrene-supported trialkylphosphine ligands is reported. These polymer-supported alkyl phosphine ligands proved to be highly active for Suzuki–Miyaura reactions and in alkoxycarbonylation reactions. The palladium loaded polymer-supported catalysts can be recycled several times with only minimal loss of catalyst activity.

## Introduction

Palladium-catalyzed cross coupling reactions are among the most commonly used methods for efficient carbon–carbon and carbon-heteroatom bond forming processes.[1] Despite their many positive attributes (regioselectivity, chemoselectivity, enantioselectivity, etc) several practical issues remain. The recovery and re-use of these valuable catalysts is highly desirable economically, although this is rarely conducted on a laboratory scale. Additionally, many homogeneous Pd-catalyzed processes result in trace metal contamination in the product which is of concern in pharmaceutical and materials applications where high purity is required, as well as heavy-metal contaminants in waste streams. Over the past few years, there has been considerable interest in the development of heterogeneous catalysts for Pd-mediated reactions where the metal is coordinated to a ligand grafted onto an inorganic or organic support.[2,3] While both tertiary phosphine (triaryl and dialkylaryl)[2–7] and N-heterocyclic carbene[7a,b] ligands have been employed, we were very surprised to find few reports on the use of immobilized *all-alkyl* tertiaryphosphines,[4,5] despite the advantages observed in homogeneous catalysis using such ligands. Polymer-supported tri*aryl*phosphine ligands have been used extensively in a range of processes.[2,4–7] In contrast, there has been only a few reports on the use of dialkylarylphosphine-supported Pd-catalysts. Becht and co-workers[6a,c] used an air-stable polymer supported dialkylarylphosphine palladium catalyst for Suzuki–Miyaura cross coupling reactions, and Sinou[7e] and co-workers reported an aryldicyclohexylphosphine supported catalyst. Both systems proved effective in activation and cross-coupling of challenging aryl chlorides. Herein we report a straightforward synthesis of dialkylbenzyl phosphines and extension to polystyrene-supported trialkyl phosphines from commercial Merrifield resin. Applications of the resin-bound phosphines in Pd-mediated Suzuki–Miyaura and carbonylation processes, including a process for their efficient recycling are also described.

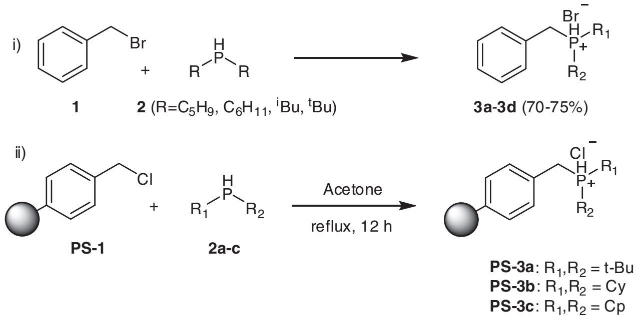
Our group has been involved in the design and syntheses of various alkylphosphine ligands and their use in homogeneous Pd-catalyzed cross-coupling reactions in a variety of media.[8] As part of this work, we investigated the reaction of benzyl bromide with secondary phosphines (Scheme 1, (i) as a direct route to dialkylbenzylphosphines. The reaction was found to proceed readily with various secondary phosphines in either acetone (12 h, reflux) or glacial acetic acid (2 h, reflux). The acetic acid protocol required a solvent switch for product isolation. Simply chilling the reaction in acetone allowed for direct crystallization of the tertiaryalkylphosphine hydrobromide salts in good overall yield. Surprisingly, no over-alkylation to yield quaternary phosphines is observed under these conditions. The free-base of the phosphine can readily be prepared or generated for reaction in situ. The success of this method prompted us to translate the protocol toward the synthesis of polymer-supported trialkylphosphine ligands utilizing Merrifield resin (Scheme 1, ii). The polystyrene immobilized ligands **PS-3a–c** were readily synthesized by addition of a dialkylphosphine **2a–c** under argon to Merrifield resin swollen in acetone or

---

* Corresponding authors. Tel.: +1 905 525 9140x27393; fax: +1 905 522 2509 (J.M.).

*E-mail address:* jmcnult@mcmaster.ca (J. McNulty).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.091

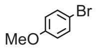
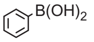
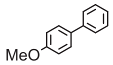
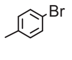
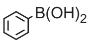
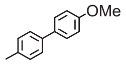
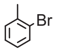
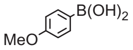
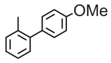
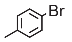
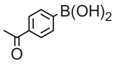
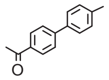
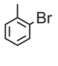
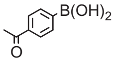
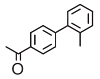


**Scheme 1.** Syntheses of tertiaryphosphine salts **3a–3d** and polymer-supported ligands PS-**3a–c**.

**Table 2**

Suzuki–Miyaura cross coupling reactions of aryl halides with phenylboronic acids using $Pd_2(dba)_3{\cdot}CHCl_3$[a]

$$\underset{\mathbf{4}}{\text{Ar-X}} + \underset{\mathbf{5}}{\text{Ar'B(OH)}_2} \xrightarrow[\text{Cs}_2\text{CO}_3\text{, 2.5 equiv. Dioxane, 70 °C}]{\text{Ligand } \mathbf{PS\text{-}3a}\text{, 4.0 mol-\%; Pd}_2\text{(dba)}_3\text{.CHCl}_3\text{, 2.0 mol-\%}} \underset{\mathbf{6}}{\text{Ar-Ar'}}$$

| Entry | R-X | Boronic acid | Product **6** | Isolated yield of **6**[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 72 |
| 2 |  |  |  | 68 |
| 3 |  |  |  | 69 |
| 4 |  |  |  | 70 |
| 5 |  |  |  | 66 |

[a] Reaction conditions. Aryl halide (0.25 mmol), Phenylboronic acid (0.28 mmol), ligand PS-**3a** (4.0 mol-%), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.0 mol-%), $Cs_2CO_3$ (0.55 mmol) in dioxane at 70 °C, 72 h.

[b] Isolated yield after column chromatography.

**Table 3**

Recycling of Pd-doped resin **PS-3a**

| Entry | PS-supported ligand PS-**3a** | Isolated yield (%) |
|---|---|---|
| 1 | Fresh | 96 |
| 2 | Recycle 1 | 94 |
| 3 | Recycle 2 | 85 |
| 4 | Recycle 3 | 80 |

acetic acid under identical conditions as described above. The reactions could be performed on a Quest-210 parallel synthesis reactor or in regular glassware on a larger scale. Solvent and excess dialkylphosphine were removed under vacuum at 80 °C. The product was washed with diethyl ether and filtered (two to three cycles) and dried to yield immobilized phosphine in quantitative yield.

The reactivity of immobilized ligand **PS-3a** was investigated using the Suzuki–Miyaura coupling reaction shown atop Table 1. The Pd-source proved non-critical and we settled on the use of $Pd(OAc)_2$ later. A palladium to ligand ratio of Pd:L (1:2) was used allowing the cross-coupling (aryl halide 1.0 equiv, boronic acid 1.2 equiv) to proceed in high yield. Reactions in ethereal solvents such as THF and dioxane were slightly superior to toluene and we settled on the use of dioxane as a general solvent. Screening of a variety of bases ($K_2CO_3$, $K_3PO_4$, $Na_2CO_3$, CsF, and $Cs_2CO_3$) showed $Cs_2CO_3$ (2.5 equiv) to be superior. In addition to 4-cyano-bromobenzene, a small panel of cross coupling reactions were conducted successfully with resin **PS-3a** using hindered and non-activated aryl bromides and phenylboronic acids with $Pd_2(dba)_3{\cdot}CHCl_3$ (Table 2).

We now turned to an investigation on the recycling of the polystyrene immobilized catalyst. Filtration of the black-polystyrene resin, washing with dioxane, and re-use initially proved to be problematic. Low conversions were observed on attempted re-use of the Pd-bound resin. Hypothesizing that this may be due to inorganic salts occluding to the resin, we introduced an aqueous wash cycle which dramatically improved the recyclability of the immobilized catalyst. When the initial reaction was completed and dioxane removed, the resin was rinsed sequentially with degassed water (2 × 3 mL), degassed ether (3 × 5 mL) and then dried under vacuum before re-swelling in dioxane and re-use. New portions of 4-cyano-bromobenzene, phenylboronic acid, and base (no new Pd) were added and the cross-coupling repeated. Using this protocol, we have successfully used one batch of supported catalyst four times with only marginal loss of efficiency, Table 3.

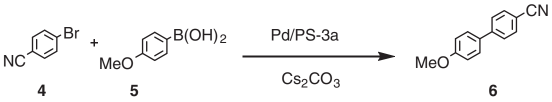
We now subjected a range of aryl halides and substituted boronic acids to the reaction, the results of which are collected in Table 4. In order to directly compare results, all reactions were stopped after 12 h and the biaryl product isolated. As expected, aryl bromides and iodides react with ease, including hindered, deactivated systems such as 2,4-dimethoxybromobenzene (Table 4, entry 3). Activation of aryl chlorides was sluggish and 4-chloroacetophenone gave only 17% isolated yield of the biaryl on reaction with phenylboronic acid under these conditions.

The analogous polystyrene bound dicyclohexylbenzyl phosphine **PS-3b** and dicyclopentylbenzyl phosphine **PS-3c** resins were also used successfully in palladium mediated Suzuki–Miyaura reactions (see Table 4a, and Table 4b in Supplementary data). The overall reactivity profile of these polystyrene-bound dialkylbenzyl phosphines, was essentially indistinguishable from **PS-3a**.

Finally, we decided to investigate Pd-mediated carbonylation reactions in order to determine the applicability of these new polystyrene bound phosphine catalysts toward a reaction involving gas-diffusion. Palladium-catalyzed carbonylation reactions are a useful method for the selective introduction of the carbonyl

**Table 1**

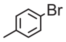
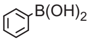
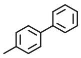
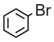
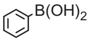
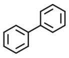
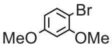
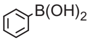
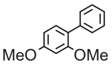
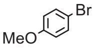
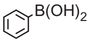
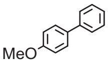
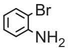
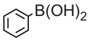
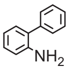
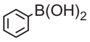
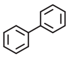
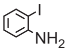
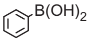
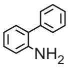
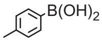
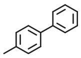
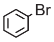
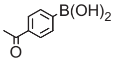
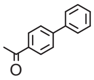
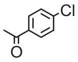
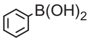
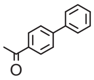
Optimization of solvent, base, and Pd-source in the Suzuki–Miyaura cross coupling reaction



| Solvent/Temp | $Pd_2(dba)_3{\cdot}CHCL_3$ (%) | $(PhCN)_2{\cdot}PdCl_2$ (%) | $(PPh_3)_2{\cdot}PdCl_2$ (%) | $Pd(OAc)_2$ (%) | $Pd(PPh_3)_4$ (%) |
|---|---|---|---|---|---|
| THF, 50 °C, 48 h | 75 | 88 | 77 | 87 | 81 |
| Toluene, 70 °C, 72 h | 70 | 90 | 88 | 89 | 89 |
| Dioxane, 70 °C, 72 h | 90 | 96 | 94 | 92 | 92 |

**Table 4**
Suzuki–Miyaura cross coupling reaction of aryl halide with phenylboronic acids[a]

$$\underset{\mathbf{4}}{\text{Ar-X}} + \underset{\mathbf{5}}{\text{Ar'B(OH)}_2} \xrightarrow[\text{Cs}_2\text{CO}_3\text{, 2.5 equiv. Dioxane, 100 °C}]{\text{Ligand } \mathbf{PS\text{-}3a}\text{, 4.0 mol-\%; Pd(OAc)}_2\text{, 2.0 mol-\%}} \underset{\mathbf{6}}{\text{Ar-Ar'}}$$

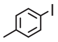
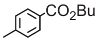
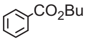
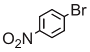
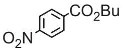
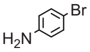
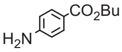
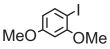
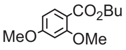
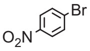
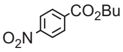
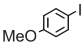
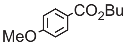
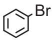
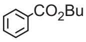
| Entry | R-X | Boronic acid | Product **6** | Isolated yield of **6**[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 85 |
| 2 |  |  |  | 90 |
| 3 |  |  |  | 78 |
| 4 |  |  |  | 82 |
| 5 |  |  |  | 80 |
| 6 |  |  |  | 94 |
| 7 |  |  |  | 86 |
| 8 |  |  |  | 83 |
| 9 |  |  |  | 88 |
| 10 |  |  |  | 17 |

[a] Reaction conditions. Aryl halide (1.00 mmol), phenylboronic acid (1.20 mmol), ligand PS-**3a** (4.00 mol-%), $Pd(OAc)_2$ (2.00 mol-%), $Cs_2CO_3$ (2.50 mmol), in dioxane at 100 °C, 12 h.

[b] Isolated yield after column chromatography.

**Table 5**
General reaction for carbonylative cross coupling using PS-phosphine ligand **PS-3a**[a]

$$\underset{\mathbf{4}}{\text{Ar-X}} + \underset{\mathbf{7}}{\text{BuOH}} \xrightarrow[\text{Cs}_2\text{CO}_3\text{, 1.5 equiv. DMF, 80 °C, 45 psi}]{\text{Ligand } \mathbf{PS\text{-}3a}\text{, 6.0 mol-\%; Pd(OAc)}_2\text{, 3.0 mol-\%}} \underset{\mathbf{8}}{\text{Ar-Ar'}}$$

| Entry | R-X | Nu | Product **8** | Isolated yield of **8**[b] (%) |
|---|---|---|---|---|
| 1 |  | 1-BuOH |  | 90 |
| 2 |  | 1-BuOH |  | 94 |
| 3 |  | 2-BuOH |  | 86 |
| 4 |  | 2-BuOH |  | 82 |
| 5 |  | 1-BuOH |  | 74 |
| 6 |  | 1-BuOH |  | 87 |
| 7 |  | 1-BuOH |  | 80 |
| 8 |  | 2-BuOH |  | 78 |

[a] Reaction conditions. Aryl halide (1.0 mmol), butanol (2.0 mmol), ligand PS-**3a** (6.0 mol-%), $Pd(OAc)_2$ (3.0 mol-%), $Cs_2CO_3$ (1.5 mmol) in DMF, 80 °C, 8 h under 45 psi CO.

[b] Isolated yield after column chromatography.

group,[9] allowing for the synthesis of esters, carboxylic acids, and amides from readily accessible aryl, vinyl, and aliphatic halides and olefins.

Heck and co-workers[10] demonstrated Palladium-catalyzed coupling of aryl halides in the presence of CO and a nucleophile (alcohol or amine) in mid 70's. These reactions have a number of synthetic applications[11] and have been used at the industrial scale.[12] A catalytic system was readily devised using the resin **PS-3a**. The carbonylation with $Pd(OAc)_2$/ligand was proved immediately successful. A catalyst system was developed using 4-nitro-1-iodobenzene as substrate and conditions were found (3.0% $Pd(OAc)_2$, 6% ligand, 1.5 equiv $Cs_2CO_3$, 2.0 equiv butanol, CO at 45 psi, DMF at 80 °C) that provided butyl 4-methylbenzoate in 90% isolated yield after 8 h. The scope of the reaction was readily extended to include aryl bromides (Table 5, entries 3, 4, and 6) using the above procedure. Under these conditions aryl chlorides remain unreactive. This is a well-known effect that, among a range of aryl chlorides, only the more electrophilically activated substrates (such as 4-chloroacetophenone) could be successfully carbonylated, and a low nucleophilicity alcohol such as trifluoroethanol is required.

In conclusion, we report a simple one step synthesis of new polymer supported trialkyl phosphine ligands from readily available Merrifield resin. Application of these toward Pd-mediated cross-coupling reactions is demonstrated, including alkoxycarbonylation reactions. The Pd-doped resins have been successfully recycled several times, providing that a critical aqueous wash step is used. Further applications of these supported catalysts to other reactions of interest are in progress.

## Acknowledgment

We thank NSERC, Cytec Canada Inc. and McMaster University for financial support of this work.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.091.

## References and notes

1. (a)*Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley: Weinheim, 2004. Vol 1&2, 349.
2. (a) Lamblin, M.; Nassar-Hardy, L.; Hierco, J. C.; Fouguet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2010**, *352*, 33–79; (b) Liu, J.; Toy, P. H. *Chem. Rev.* **2009**, *109*, 815–838; (c) Choi, M. K. W.; He, H. S.; Toy, P. H. *J. Org. Chem.* **2003**, *68*, 9831–9834.
3. (a) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173; (b) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679; (c) Felin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679–2690.
4. (a) Zhou, W. J.; Wang, K. H.; Wang, J. X.; Huang, D. F. *Eur. J. Org. Chem.* **2010**, *3*, 416–419; (b) Buchmeiser, M. R. *Chem. Rev.* **2009**, *109*, 303–321; (c) Heeten, R. D.; Swennenhuis, B. H. G.; Van Leeuwen, P. W. N. M.; De Vries, J. G.; Kamer, P. C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6602–6605; (d) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *121*, 11101–11107; (e) Boussie, T. R.; Coutard, C.; Turner, H.; Murphy, V.; Power, T. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3272–3275; (f) Naguyen, S. T.; Grubbs, R. H. *Organomet. Chem.* **1995**, *497*, 195–200; (g) Bergbreiter, D. E.; Chen, B.; Lynch, T. J. *J. Org. Chem.* **1983**, *48*, 4179–4186.
5. (a) Bai, L.; Wang, J.-X. *Adv. Synth. Catal.* **2008**, *350*, 315–320; (b) Schweizer, S.; Becht, J.-M.; Le Drian, C. *Adv. Synth. Catal.* **2007**, *349*, 1150–1158; (c) Bai, L.; Wang, J.-X. *Curr. Org. Chem.* **2005**, *9*, 535–553; (d) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217–3274; (e) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820–3827.
6. (a) Schweizer, S.; Becht, J.-M.; Le Drian, C. *Tetrahedron* **2010**, *66*, 765–772; (b) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed. Chem.* **2009**, *48*, 2708–2710; Schweizer, S.; Becht, J.-M.; Le Drian, C. *Org. Lett.* **2007**, *9*, 3777–3780; (c) Uozumi, Y. *Top. Curr. Chem.* **2004**, *242*, 77–112; (d) Brease, S.; Kirchhoff, J. H.; Keobberling, J. *Tetrahedron* **2003**, *59*, 885–939; (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–2469.

7. (a) Zeng, X. M.; Zhang, T. X.; Qin, Y. C.; Wei, Z. J.; Luo, M. M. *Dalton Trans.* **2009**, 8341–8348; (b) Lee, D. H.; Kim, J. H.; Jun, B. H.; Kang, H.; Park, J.; Lee, Y. S. *Org. Lett.* **2008**, *10*, 1609–1612; (c) Kantam, M. L.; Roy, M.; Roy, S.; Sreedhar, B.; Madhavendra, S. S.; Choudary, B. M.; De, R. L. *Tetrahedron* **2007**, *63*, 8002–8009; (d) Gallon, B. J.; Kojima, R. W.; Kaner, R. B.; Diaconescu, P. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7251–7254; (e) Glegola, K.; Framery, E.; Pietrusiewicz, K. M.; Sinou, D. *Adv. Synth. Catal.* **2006**, *348*, 1728–1733; (f) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Scordia, V. J. M. *Dalton Trans.* **2005**, 991–995; (g) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661–8664.
8. (a) Ullah, E.; McNulty, J.; Kennedy, C.; Robertson, A. *Org. Biomol. Chem.* **2011**, *9*, 4421–4424; (b) Ullah, E.; McNulty, J.; Larichev, V.; Robertson, A. *Eur. J. Org. Chem.* **2010**, 6824–6830; (c) Ullah, E.; McNulty, J.; Robertson, A. *Tetrahedron Lett.* **2009**, *50*, 5599–5601; (d) McNulty, J.; Nair, J. J.; Robertson, A. *Org. Lett.* **2007**, *9*, 4575–4578; (e) McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A. *Eur. J. Org. Chem.* **2007**, *9*, 1423–1428; (f) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. *Chem. Eur. J.* **2006**, *12*, 9314–9322; (g) McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. *Tetrahedron Lett.* **2005**, *46*, 3641–3644; (h) Gerritsma, D. A.; Robertson, A.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 7629–7631; (i) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. L. *Chem. Commun.* **2002**, 1986–1987.
9. (a) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119; (b) Mori, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, pp 2663–2682; (c) Luh, T. Y.; Leung, M.; Wong, K. T. *Chem. Rev.* **2000**, *100*, 3187–3202; (d) Beller, M. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley: Weinheim, Germany, 2002; Vol. 1, pp 145–156. 2nd ed; (e) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal.* **1995**, *104*, 17.
10. (a) Moser, W. R.; Wang, A. W.; Kildahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816–2820; (b) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115–4127; (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764; (d) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326; (e) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.
11. (a) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107; (b) Rucklidge, A. J.; Morris, G. E.; Slawin, A. M. Z.; Cole-Hamilton, D. J. *Helv. Chim. Acta* **2006**, *89*, 1783–1800; (c) Jimenez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *Inorg. Chem. Commun.* **2005**, *8*, 878–881; (d) Ooka, H.; Inoue, T.; Itsuno, S.; Tanaka, M. *Chem. Commun.* **2005**, 1173–1175; (e) Rodriguez, C. J.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun.* **2004**, 1720–1721; (f) Rucklidge, A. J.; Eastham, G. R.; Cole-Hamilton, D. J. Int. Pat. WO2004050599, 2004.; (g) Eastham, G. R.; Tooze, R. P.; Kilner, M.; Foster, D. F.; Cole-Hamilton, D. J. *J. Chem. Soc. Dalton Trans.* **2002**, 1613–1617; (h) Mizushima, E.; Hayashi, T.; Tanaka, M. *Green Chem.* **2001**, *3*, 76–79.
12. (a) Tremblay, J. F. *Chem. Eng. News* **2008**, *86*, 8. November 17th; (b) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101; (c) New MMA Technology, European Chem. News, Oct. 30th -Nov. 5th 2000, 20.