ORGANIC
LETTERS

2013
Vol. 15, No. 8
1886–1889

# Ligand- and Base-Free Pd(II)-Catalyzed Controlled Switching between Oxidative Heck and Conjugate Addition Reactions

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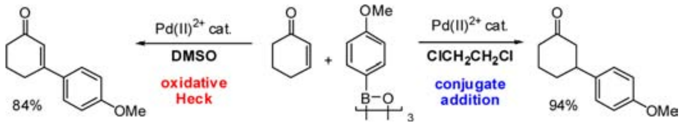
**Received February 26, 2013**

## ABSTRACT



**A simple change of solvent allows controlled and efficient switching between oxidative Heck and conjugate addition reactions on cyclic Michael acceptor substrates, catalyzed by a cationic Pd(II) catalyst system. Both reactions are ligand- and base-free and tolerant of air and moisture, and the controlled switching sheds light on some of the factors which favor one reaction over the other.**

The Pd(0)-catalyzed Mizoroki−Heck reaction is one of the most widely used C−C bond forming reactions in organic synthesis.[1] However, Pd(0)-catalyzed Heck conditions generally do not work as well with *cyclic* enones due to the tendency to form conjugate addition products instead, as well as being stereochemically precluded from undergoing the final step in the traditional Heck cycle: the *syn* $\beta$-H elimination.[2] In recent years, the Pd(II)-catalyzed boron *oxidative* Heck reaction[3] has emerged as a promising new method which enables Heck-type couplings on cyclic systems. Generally, a ligand, base, or both are required, and the reactions can be carried out under mild conditions in air. Nevertheless, reports using cyclic enone substrates are still rare,[4] and obtaining either the oxidative Heck or conjugate addition product selectively with cyclic enones can still pose a challenge.[5] Indeed, the conditions utilized for Pd(II)-catalyzed conjugate addition reactions[6,7] can often appear quite similar to the oxidative Heck conditions, prompting us to question the factors which might favor one reaction over its competitor. As far as we are aware, there are no reported studies on the Pd(II)-catalyzed switching between oxidative Heck and conjugate addition reactions[8,9] or reports on factors which might influence the formation of one product over the other.

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(1) Review on Pd-catalysis: Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; John Wiley & Sons: Chichester, U.K., 2004.

(2) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433.

(3) Review: (a) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. Selected papers: (b) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85. (c) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313. (d) Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 1484. (e) Andappan, M. M. S.; Nilsson, P.; Von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212. (f) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. (g) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270. (h) Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496. (i) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981. (j) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231. (k) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980. (l) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933. (m) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (n) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424. (o) Xiong, D.-C.; Zhang, L. H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709. (p) Sun, P.; Zhu, Y.; Yang, H.; Yan, H.; Lu, L.; Zhang, X.; Mao, J. *Org. Biomol. Chem.* **2012**, *10*, 4512. (q) He, Z.; Kirchberg, S.; Frohnlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3699. (r) Crowley, J. D.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12092.

(4) For example, see: (a) Gottumukkala, A. L.; Teichert, J. F.; Heijnen, D.; Eisink, N.; van Dijk, S.; Ferrer, C.; van den Hoogenband, A.; Minnaard, A. J. *J. Org. Chem.* **2011**, *76*, 3498. (b) Li, Y.; Qi, Z.; Wang, H.; Fu, X.; Duan, C. *J. Org. Chem.* **2012**, *77*, 2053 and ref 3m.

(5) For example, see: Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, *694*, 1325.

(6) For reviews, see: (a) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547. (b) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807. (c) Berthon, G.; Hayashi, T. Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, 2010.

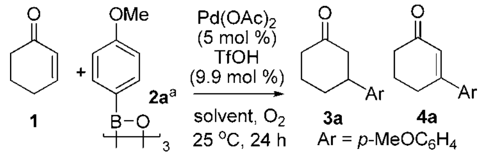
10.1021/ol400539h

We have recently reported a mild and ligand-free cationic Pd(II)$^{2+}$ system for diastereoselective conjugate addition reactions to sterically hindered cyclic enones.[10] As part of our ongoing studies to evaluate the utility of the new ligand-free catalyst system, we were keen to address the issue of competition between the oxidative Heck and conjugate addition reactions on cyclic enones. Thus, our aims were twofold: to successfully and efficiently control *switching* between the two outcomes by changing a variable in the reaction, thereby shedding some light on the *factors* which influence the switching.

With the conjugate addition conditions for the formation of **3** already in hand (entry 1, Table 1), our investigations commenced with screening of reaction conditions to switch the outcome fully to oxidative Heck product **4** (Table 1). An *in situ* method for generating the cationic Pd(OTf)$_2$ catalyst was used in this screen, utilizing Pd(OAc)$_2$ and TfOH. Pleasingly, a clear shift toward the oxidative Heck product **4** is observed upon adoption of more polar solvents, although conversions are poor (entries 2–9). Finally, DMSO was found to change the outcome of the reaction successfully to favor only **4** (entry 9). Warming to 50 °C pushed the reaction to completion, yielding **4** in a good 84% yield, thereby successfully obtaining a complete switch in reactivity from conjugate addition **3** (entry 1) to oxidative Heck **4** (entry 10) by a simple change of solvent ($ClCH_2CH_2Cl$ to DMSO).

With these pleasing results in hand, substitution around the cyclohexenone core was investigated next (Table 2, entries 3–8). 6-Substituted cyclohexenone **5** undergoes the conjugate addition (entry 3) as well as oxidative Heck reactions smoothly (entry 4). 5-Substituted cyclohexenone **8** undergoes conjugate addition in good yield (75%, entry 5), but an oxidative Heck reaction under the usual conditions produced a poor 25% conversion. Fortunately, reversing the stoichiometry (from 1:2 **8**/**2** to 3:1 **8**/**2**) and setting the temperature at 70 °C successfully promotes the oxidative Heck reaction (60%, entry 6). Moving the substituent even closer to the reactive alkene (**11**) does not hinder the conjugate addition, but clearly slows down the oxidative Heck reaction (entries 7–8). With the latter, dimerization of the arylboroxine becomes competitive, resulting in only a low conversion to the desired **13**. This is perhaps unsurprising as $\gamma$-substituted cyclohexenones are notoriously difficult substrates for any Heck-type reaction.[2]

**Table 1.** Initial Studies: Conditions for Switching from Pd(II)-Catalyzed Conjugate Addition to Oxidative Heck Reaction



| entry | solvent | yield **3** (%)[b] | yield **4** (%)[b] |
|---|---|---|---|
| **1** | **$ClCH_2CH_2Cl$** | **94**[c] | – |
| 2 | $ClCH_2CH_2Cl$ + DMF (4 equiv) | 79[c] | 20[c] |
| 3 | DMF | – | trace |
| 4 | acetone | – | 14 |
| 5 | MeCN | trace | trace |
| 6 | DMA[d] | trace | trace |
| 7 | MeOH | – | 4 |
| 8 | NMP[e] | 12 | 4 |
| 9 | DMSO | – | 33[c] |
| **10**[f] | **DMSO** | – | **84**[c] |

[a] Commercial arylboronic acid was heated under vacuum to generate boroxine. [b] Determined by $^1$H NMR analysis of crude mixture, unless otherwise stated. [c] Isolated yield. [d] Dimethyl acetamide. [e] *N*-Methylpyrrolidone. [f] 50 °C, 48 h.

Next, more electron-rich alkene substrates were evaluated (entries 9–14). With these systems, it was found that the premade cationic catalyst (MeCN)$_4$Pd(OTf)$_2$ (**B**) often performs better. Thus, the switching from conjugate addition to oxidative Heck reaction proceeds smoothly with lactone **14** (entries 9–10). Dihydropyridones[11] **17** and **20** also switch between the two reactions smoothly, although the oxidative Heck reaction does require portionwise addition of the catalyst and **2a** to push the reaction to completion (entries 11–14). Changing the ring size from six-membered systems to five-membered cyclopentenone **23** results in a smooth conjugate addition reaction (entry 15), but surprisingly, switching to an oxidative Heck reaction in DMSO is now no longer as efficient (1:1 **24**/**25**, entry 16).

Having explored the alkene substrate scope, we turned our attention to the arylboroxine scope (Table 3). Premade (MeCN)$_4$Pd(OTf)$_2$ catalyst was found to be more general for the range of arylboroxines studied and was thus employed in the general procedure. The conjugate addition

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(7) For selected Pd(II)-catalyzed conjugate additions, see: (a) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. G.; Minnaard, A. J. *Chem.—Eur. J.* **2012**, *18*, 6907. (b) Lan, Y.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 4905. (c) Kikushima, K.; Holder, J. C.; Gatti, M.; Stolz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (d) Brozek, L. A.; Sieber, J. D.; Morken, J. P. *Org. Lett.* **2011**, *13*, 995. (e) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536. (f) Xu, Q.; Zhang, R.; Zhang, T.; Shi, M. *J. Org. Chem.* **2010**, *75*, 3935. (g) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 7167. (h) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2007**, *36*, 1442. (i) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, *349*, 1759. (j) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651. (k) Gini, F.; Hessen, B.; Minaard, A. J. *Org. Lett.* **2005**, *7*, 5309. (l) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317. (m) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.

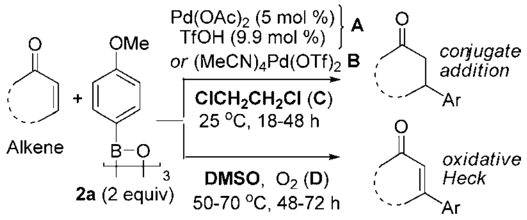
(8) In contrast, there are several investigations on the Rh-catalyzed counterparts. For example, for cyclic alkene substrates, see: (a) Kuuloja, N.; Vaismaa, M.; Franzén, R. *Tetrahedron* **2012**, *68*, 2313. Acyclic: (b) Zou, G.; Guo, J.; Wang, Z.; Huang, W.; Tang, J. *Dalton Trans.* **2007**, 3055. (c) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774. (d) Noël, T.; Gök, Y.; Van der Eycken, J. *Tetrahedron: Asymmetry* **2010**, *21*, 540. (e) Amengual, R.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905. (f) Zou, G.; Wang, Z.; Zhu, J.; Tang, J. *Chem. Commun.* **2003**, 2438.

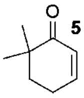
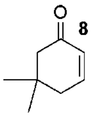
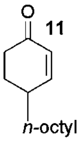
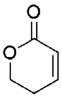
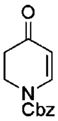
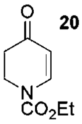
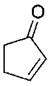
(9) For a related, but mechanistically distinct, study using aryl iodide substrates and Pd(0)-catalysis to switch between Pd(0) Mizoroki–Heck and conjugate additions, see: (a) Gottumukkala, A. L.; de Vries, J. G.; Minnaard, A. J. *Chem.—Eur. J.* **2011**, *17*, 3091 and references cited therein. See also: (b) Fall, Y.; Doucet, H.; Santelli, M. *Tetrahedron* **2009**, *65*, 489. Intramolecular Pd(0): (c) Friestad, G. K.; Branchaud, B. P *Tetrahedron Lett.* **1995**, *36*, 7047.

(10) Jordan-Hore, J. A.; Sanderson, J. N.; Lee, A.-L. *Org. Lett.* **2012**, *14*, 2508.

(11) For conjugate additions to dihydropyridones see: Xu, Q.; Zhang, R.; Zhang, T.; Shi, M. *J. Org. Chem.* **2010**, *75*, 3935.

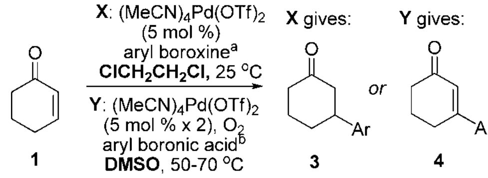
**Table 2.** Alkene Substrate Scope



| entry | alkene | catalyst, conditions | conj. add. or ox. Heck | product (%)[a] |
|---|---|---|---|---|
| 1 | **1** | A, C | conj. add. | **3a** 94% |
| 2 | **1** | A, D | ox. Heck | **4a** 84% |
| 3 |  **5** | A, C | conj. add. | **6** 76% |
| 4 | **5** | A, D | ox. Heck | **7** 57% |
| 5 |  **8** | A, C | conj. add. | **9** 75% |
| 6[b, c] | **8** | A, D | ox. Heck | **10** 60% |
| 7[c] |  **11** | A, C | conj. add. | **12** 94%<br>8:1 dr |
| 8[c] | **11** | A, D | ox. Heck | **13** 38%<br>conv |
| 9[c, d] |  **14** | B, C | conj. add. | **15** 68% |
| 10[c] | **14** | A, D | ox. Heck | **16** 66% |
| 11[c] |  **17** | B, C | conj. add. | **18** 88% |
| 12[c, e] | **17** | B, D | ox. Heck | **19** 50% |
| 13[c] |  **20** | B, C | conj. add. | **21** 60% |
| 14[c, e] | **20** | B, D | ox. Heck | **22** 80% |
| 15 |  **23** | A, C | conj. add. | **24** 61% |
| 16 | **23** | A, D | 1:1 | **25** 32%<br>(ox. Heck) |

[a] Isolated yield. [b] 0.33 equiv of **2a**. [c] $NaNO_3$ added (1–2 equiv).[10] [d] 3 equiv of **2a**. [e] 10 + 5 mol % cat., 2 + 0.5 equiv of **2a**.

**Table 3.** Arylboroxine/Boronic Acid Scope



| entry | aryl | cond. | yield (%)[c] |
|---|---|---|---|
| 1 | Ph | **X** | **3b** 77 |
| 2 | *p*-$HOC_6H_4$ | **X** | **3c** 67 |
| 3 | *m*-$MeC_6H_4$ | **X** | **3d** 68 |
| 4 | *o*-$MeC_6H_4$ | **X** | **3e** 76 |
| 5 | 2-naphthalene | **X** | **3f** 84 |
| 6 | 2-fluorene | **X** | **3g** 51 |
| 7 | *m*-$ClC_6H_4$ | **X** | **3h** 82 |
| 8 | *m*-$MeO_2CC_6H_4$ | **X** | **3i** 75 |
| 9 | *m*-$O_2NC_6H_4$ | **X** | **3j** 59 |
| 10[d] | *p*-$BrC_6H_4$ | **X** | **3k** 71 |
| 11[e] | Ph | **Y** | **4b** 68 |
| 12[e] | *p*-$HOC_6H_4$ | **Y** | **4c** 60 |
| 13 | *m*-$MeC_6H_4$ | **Y** | **4d** 66 |
| 14 | *o*-$MeC_6H_4$ | **Y** | **4e** 57 |
| 15 | 2-naphthalene | **Y** | **4f** 68 |
| 16 | 2-fluorene | **Y** | **4g** 48[f] |
| 17 | *m*-$ClC_6H_4$ | **Y** | **4h** 53[g] |
| 18 | *m*-$MeO_2CC_6H_4$ | **Y** | **4i** 43[g] |
| 19 | *m*-$O_2NC_6H_4$ | **Y** | **4j** 50% conv[g] |
| 20 | *p*-$BrC_6H_4$ | **Y** | **4k** 24[g] |
| 21 | *m*-$MeC_6H_4$ | **Y**[h] | **4d** 66 |
| 22 | *m*-$MeC_6H_4$ | **Y**[e] | **4d** 46 |

[a] Commercial boronic acid was heated under vacuum to generate boroxine. 2 equiv used. $NaNO_3$ (2 equiv) added.[10] [b] Arylboronic acid recrystallized from water. 2 × 2 equiv used. [c] Isolated yield. [d] $O_2$ atm. [e] Arylboroxine used. [f] 34% **3g** also isolated. [g] Three portions of 5 mol % catalyst. [h] Commercial arylboronic acid + water (1.5 equiv).

reaction to form **3a**–**3j** progressed smoothly for a range of aryls, including those that were electron-rich, electron-poor, and *para*-, *meta*-, and *ortho*-substituted (entries 1–10). Even easily oxidizable 2-fluorene performs reasonably well (entry 6).

The oxidative Heck reaction, however, proved more challenging and was initially hampered by poor or incomplete conversions. After optimization, we found that portionwise addition of the catalyst (2 × 5 mol %) and arylboroxine (2 × 2 equiv) improved the yields for Ar = Ph and *p*-$HOC_6H_4$ (entries 11–12). However, the conversions were still low for other aryls (e.g., entry 22). At this point, we discovered that while the conjugate addition reactions require aryl*boroxines* (formed by heating commercial "boronic acid" under vacuum),[10] the oxidative Heck reaction behaves in the opposite manner, performing better when arylboronic acids (formed by recrystallization from water) are used. This is presumably why the different aryls behave differently when used straight out of a commercial bottle, as they tend to lie on different ends of the arylboronic acid/boroxine equilibrium[12] and may also hydrate at different rates in the DMSO solution. Thus, using freshly recrystallized arylboronic acids and optimized general conditions **Y**, the oxidative Heck was successfully carried out using a range of aryls: *o*-, *m*-, and *p*-substitutions (entries 13–18) as well as electron-donating (entries 12–14), polycyclic aromatic (entries 15–16), and electron-withdrawing groups (entries 17–18). Of these, only the

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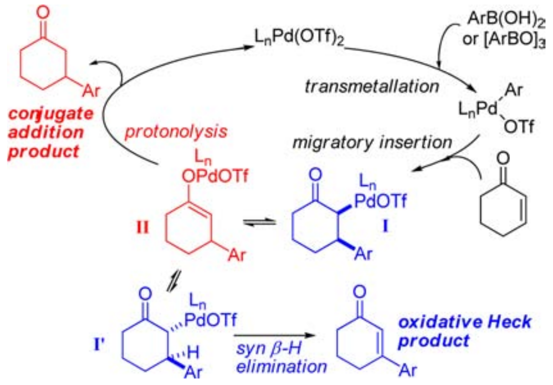
(12) Korich, A. L.; Iovine, P. M. *Dalton Trans.* **2010**, *39*, 1423.

large 2-fluorene reaction struggled to produce an efficient switch (48% **4g**, 34% of **3g**, entry 16). Reactions with *m*-$O_2NC_6H_4$ and *p*-$BrC_6H_4$ did not proceed to full conversion; in these two cases Ar−Ar homocoupling dominates (entries 19−20). Finally, we found that using commercial "arylboronic acid" straight from the bottle, but with 1.5 equiv of water added to the reaction (which presumably generates arylboronic acid *in situ*), performs just as well as using freshly recrystallized arylboronic acid (entry 21 vs 13) and far better than with arylboroxine (entry 22).

**Scheme 1.** Proposed Mechanism of the Oxidative Heck and Conjugate Addition Reactions



The mechanism of the two reactions is thought to diverge after the transmetalation and migratory insertion steps (Scheme 1).[13] Intermediate **I** can either undergo *β*-H elimination to produce the oxidative Heck product or protonolysis (either directly or more often described as *via* Pd-enolate **II**) to produce the conjugate addition product. In order to promote the oxidative Heck reaction over conjugate addition, it is clear that the *β*-H elimination must be facilitated. We thus propose that the solvent switch from nonpolar $ClCH_2CH_2Cl$ to polar DMSO causes such a dramatic switch in the selectivity due to two possible reasons. First, in our "ligand-free" cationic Pd(II) conditions, the polar and more coordinating DMSO must be stabilizing the cationic Pd center [see Supporting Information for $(DMSO)_4Pd(OTf)_2$ crystal structure],[14] and possibly affecting the equilibrium between **I**, **II**, and **I′**. Second, since *syn β*-H elimination is not possible in cyclic intermediates such as **I**, it is usually assumed that epimerization of the α-C in **I** via enolization to form **I′** must take place in order to allow for the *syn*-*β*-H elimination required to form the oxidative Heck product. Following this argument, the use of polar and relatively basic DMSO solvent[15] must be facilitating the epimerization (**I**→**I′**) compared to nonpolar $ClCH_2CH_2Cl$.[16]

A third possibility is that the DMSO conditions allow a conjugate addition followed by oxidation,[17] rather than a true oxidative Heck reaction. To rule out this possibility, a control reaction was carried out whereby the conjugate addition product **3a** was subjected to the DMSO oxidative Heck conditions. Only a trace of oxidative Heck product **4a** is formed after 2 days,[18] confirming that **4a** is *not* formed via **3a** and that the reactions in DMSO shown in Tables 1−3 are true oxidative Heck reactions.

In conclusion, we have developed an efficient way of switching between oxidative Heck and conjugate addition reactions on cyclic alkenes using a *simple switch of solvent*, in a base- and ligand-free $Pd(II)^{2+}$ system. In doing so, we have discovered several important subtleties regarding the competition between these two reactions. First, the conjugate addition requires arylboroxines whereas the oxidative Heck reaction performs better with arylboronic acids under our reaction conditions. Second, more polar solvents promote the oxidative Heck reaction over conjugate addition. We hope our studies shed some light onto the often encountered, but rarely investigated, competition between conjugate addition and oxidative Heck reactions in Pd(II)-catalyzed systems, thus leading the way for more selective reactions in the future.

**Acknowledgment.** We thank the Leverhulme Trust (F/00 276/O), EPSRC (S.E.W.), Nuffield Undergraduate Bursary (L.P.), and Erasmus (J.B.) for funding; EPSRC NMSCC for analytical services; Johnson Matthey for $Pd(OAc)_2$; and Georgina M. Rosair (Heriot-Watt University) for crystallography.

**Supporting Information Available.** Experimental procedures, spectroscopic data, and NMR spectra for all new compounds; crystal structure of $(DMSO)_4Pd(OTf)_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See ref 6c, p 57.

(14) When 4 equiv of DMSO are added to $(MeCN)_4Pd(OTf)_2$, $(DMSO)_4Pd(OTf)_2$ is produced, with 2 *S*-bound and 2 *O*-bound DMSO (*cis*). This complex is catalytically active in the oxidative Heck reaction.

(15) Jessop, P. G. *Green Chem.* **2011**, *13*, 1391.

(16) When entry 10, Table 1 is carried out with the catalyst made *in situ* in DMSO (40 mol %) and then diluted with $ClCH_2CH_2Cl$ as the solvent, the resulting poor 3.4:1 **3**/**4** ratio implies that, for a full switch to **4**, DMSO is also required as a solvent rather than simply for producing $(DMSO)_4Pd(OTf)_2$.

(17) Oxidation: Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566.

(18) See Supporting Information for further details.

The authors declare no competing financial interest.