

## Studies on the Heck Reaction with Alkenyl Phosphates: Can the 1,2-Migration Be Controlled? Scope and Limitations

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**Abstract:** A catalyst system was identified which promotes the Heck coupling of nonactivated vinyl phosphates with electron deficient alkenes providing a new entry to diene products from simple and readily accessible starting materials. In contrast to our earlier work exploiting  $P(t\text{-Bu})_3$  as the ligand in the presence of  $PdCl_2(COD)$ , the application of Buchwald's dialkylbiarylphosphines, X-Phos, effectively promoted the vinylic substitution with a wide range of alkenyl phosphates in the presence of 10 equiv of lithium chloride. Importantly, these reaction conditions suppressed 1,2-migration of the alkenyl palladium(II) intermediate. Further studies are also reported with the catalytic system which encourages isomerization in order to determine the range of vinyl phosphates that may participate in these coupling reactions. The extent of the 1,2-migration was dependent on the C1-substituent where best results were noted for substrates possessing a C1-alkyl quaternary carbon. Hence, with certain members of this class of alkenyl phosphates either the migrated or nonmigrated Heck products may be preferentially synthesized by selection of the phosphine ligand. Finally, competition experiments between an unactivated aryl chloride and a vinyl phosphate with a palladium catalyst possessing either X-Phos or  $P(t\text{-Bu})_3$  as ligand demonstrated the ability to carry out Heck coupling reactions selectively with the aryl halide. Oxidative addition of the metal catalyst into the aryl chloride bond rather than the C–O bond of the alkenyl phosphate is therefore preferred.

### Introduction

The palladium(0)-catalyzed arylation or vinylation of olefins, more commonly referred to as the Heck reaction, represents a well-established method for carbon–carbon bond formation in organic synthesis on both a laboratory and industrial scale.<sup>1–4</sup> So far the majority of the published work concerning Heck reactions has focused on the use of either aryl/vinyl iodides or

bromides coupled to olefins bearing an electron withdrawing substituent such as  $-\text{CO}_2\text{R}$ ,  $-\text{Ph}$ , or  $-\text{CN}$ . As with other cross coupling reactions, extensive efforts particularly from the groups of Fu,<sup>5</sup> Hartwig,<sup>6</sup> Beller,<sup>7</sup> and Herrmann<sup>8</sup> and others have been made in recent years to include aryl chlorides as a viable Heck reagent notably due to the considerably lower commercial costs of such compounds compared to the other aryl halides.<sup>9,10</sup>

Aryl and alkenyl triflates or nonaflates also represent valuable coupling partners for the Heck reaction in couplings with both electron deficient and electron rich olefins.<sup>2h,11,12</sup> In this way, the repertoire of coupling reagents can be expanded to include

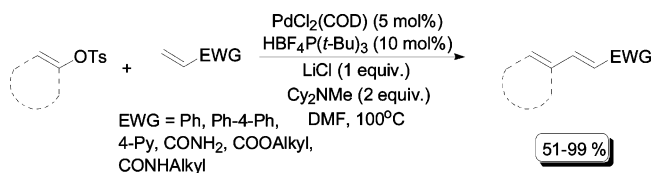
- (1) (a) Heck, R. F. *Synlett* **2006**, 2855. (b) Heck, R. F.; Dieck, H. A. *J. Am. Chem. Soc.* **1974**, *96*, 1133. (c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505. (d) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (e) Heck, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 6896. (f) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
- (2) For reviews of the Heck reaction, see: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; J. Wiley & Sons: New York, 2002. (b) Whitcombe, N. J.; Hii, K. K. M.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (d) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; J. Wiley & Sons, Ltd.: 2000; Chapter 3. (e) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23. (f) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (g) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, p 153. (h) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (i) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (j) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.
- (3) For reviews on the applications of the Heck reaction in natural product total synthesis, see: (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; VCH: New York, 2003. (b) Dounay, A. M.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1.
- (4) For reviews on the commercial applications of the Heck reaction, see: (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101. (c) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.

- (5) (a) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (d) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
- (6) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123.
- (7) (a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357. (b) Beller, M.; Zapf, A. *Synlett* **1998**, 792. (c) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589. (d) Zapf, A.; Beller, M. *Chem. Eur. J.* **2001**, *7*, 2908. (e) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031.
- (8) (a) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (b) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371. (c) Herrmann, W. A.; Böhm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141. (d) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (e) Herrmann, W. A.; Böhm, V. P. W. *Chem. Eur. J.* **2000**, *6*, 1017. (f) Frey, G. D.; Reisinger, C.-P.; Herdtweck, E.; Herrmann, W. A. *J. Organomet. Chem.* **2005**, *690*, 3193.
- (9) For reviews on the use of aryl chlorides in palladium(0)-catalyzed couplings, see: (a) Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 431. (b) Littke, A. F.; Fu, G. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

phenols and alkyl ketones. Nevertheless, there are some concerns which limit the use of aryl and alkenyl triflates or nonaflates. Instability issues as well as the requirement of expensive triflating and nonaflating agents for the synthesis of the Heck precursors are major disadvantages, and hence alternative and less costly means for activating phenols or alkyl ketones would therefore be welcomed.<sup>13–19</sup>

As a potential substitute for alkenyl triflates and nonaflates, the corresponding tosylates and phosphates have proven their worth in a variety of cross coupling reactions such as the Stille,<sup>20</sup>

## Scheme 1

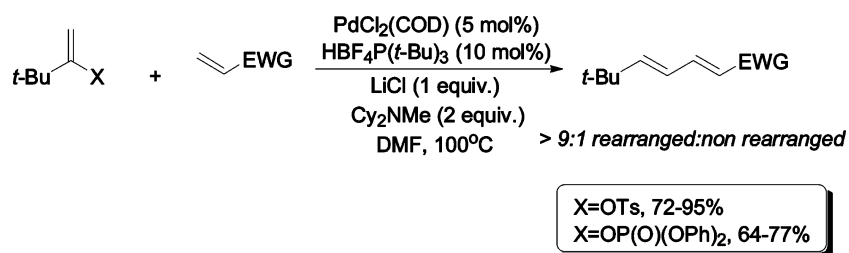


Negishi,<sup>21</sup> Suzuki,<sup>20a,22</sup> Kumada,<sup>23</sup> Sonogashira,<sup>20a,24</sup> amination/amidation (Buchwald–Hartwig),<sup>23c,25</sup> and carbonyl enolate arylations.<sup>22e</sup> However, in many instances efforts were concentrated on the use of activated vinyl tosylates and phosphates such as  $\alpha,\beta$ -unsaturated esters and ketones or  $\alpha$ -heteroatom substituted olefins, as the oxidative addition step in these systems with the common palladium(0) catalysts employing aryl phosphine ligands proceed under relatively mild conditions. We and others have also recently demonstrated the similar exploitation of activated vinyl tosylates and mesylates as a substitute for the corresponding triflates in the Heck reaction with vinyl amides and ethers.<sup>26</sup>

Considerable efforts have been directed over the past few years to increase the scope of these coupling reactions with nonactivated alkenyl tosylates and phosphates, as well as the complementary derivatives of phenols. Two approaches have been adopted to overcome the challenging step of the catalytic cycle represented by the oxidative addition into the C–O bond: either Pd(0)-centered catalysts possessing bulky electron rich phosphine ligands that facilitate the preliminary step of the catalytic cycle have been applied<sup>21a,b,22d,h,23a–c,24a,25a,b</sup> or alternative more reactive transition metal systems such as Ni(0) complexes were explored.<sup>21c,22a,b,e,j,l,m,23d–f</sup> In these difficult cases, less attention has been devoted to the Heck reaction, which may also be related to the dissimilarities in reaction mechanisms between the different transition metal catalyzed coupling reactions. For example, whereas Ni(0)-based catalyst systems can promote Suzuki cross couplings between aryl and vinyl tosylates or phosphates with aryl boronic acids under mild

- (10) (a) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152. (a) Datta, G. K.; von Schenk, H.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 3896. (b) Pröckl, S. S.; Kleist, W.; Gruber, M. A.; Köhler, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881. (c) Consorti, C. S.; Ebeling, G.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2004**, *346*, 617. (d) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495. (e) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2002**, *344*, 172. (f) Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990. (g) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (h) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 11504. (i) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995. (j) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (k) Morales-Morales, D.; Redón, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619. (l) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481.
- (11) For some representative examples of the use of triflates in Heck reactions, see: (a) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997. (b) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751. (c) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (d) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (e) Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521. (f) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558. (g) Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302. (h) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *21*, 2271.
- (12) For examples of the use of nonaflates in the Heck reaction, see: (a) Högermeier, J.; Reißig, H.-U.; Brüdgam, I.; Hartl, H. *Adv. Synth. Catal.* **2004**, *346*, 1868. (b) Lyapkalo, I. M.; Webel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2002**, 3646. (c) Lyapkalo, I. M.; Webel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2001**, 4189. (d) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. (e) Bräse, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545.
- (13) For examples of decarboxylative Heck reactions, see: (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.
- (14) For examples of decarbonylative Heck reactions, see: (a) Andrus, M. B.; Liu, J. *Tetrahedron Lett.* **2006**, *47*, 5811. (b) Andrus, M. B.; Liu, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1095. (c) Großen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1237.
- (15) For examples of Heck reactions with diazonium salts, see: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. (b) Burtoloso, A. C. B.; Garcia, A. L. L.; Miranda, K. C.; Corriea, C. R. D. *Synlett* **2006**, 18, 3145. (c) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.* **2006**, *47*, 1325. (d) Masllorens, J.; Bouquillon, S.; Roglans, A.; Hémin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822. (e) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514. (f) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079. (g) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2002**, *8*, 3901.
- (16) For examples of Heck reactions with anhydrides, see: (a) Lim, K.-C.; Hong, Y.-T.; Kim, S. *Synlett* **2006**, 12, 1851. (b) Gooßen, L. J.; Paetzold, J.; Winkel, L. *Synlett* **2002**, 10, 1721. (c) Schmidt, A. F.; Smirnov, V. V. *Kinet. Catal.* **2002**, *43*, 195. (d) Tucker, C. E.; de Vries, J. G. *Top. Catal.* **2002**, *1*, 111. (e) Schmidt, A. F.; Smirnov, V. V. *Kinet. Catal.* **2000**, *41*, 743. (f) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 662.
- (17) For an example of a Heck reaction with telluronium salts, see: Hirabayashi, K.; Nara, Y.; Shimizu, T.; Kamigata, N. *Chem. Lett.* **2004**, 33, 1280.
- (18) For examples of Heck reactions with aryl chlorides, see: (a) Sugihara, T.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2005**, *46*, 8269. (b) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Adv. Synth. Catal.* **2004**, *346*, 1765. (c) Andrus, M. B.; Liu, J.; Meredith, L.; Nartey, E. *Tetrahedron Lett.* **2003**, *44*, 4819. (d) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4672.
- (19) For examples of desulfonylative Heck reactions, see: (a) Dubbaka, S. R.; Vogel, P. *Chem. Eur. J.* **2005**, *11*, 2633. (b) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, 30, 975.
- (20) (a) Steinhuebel, D.; Baxter, J. M.; Palucki, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 10124. (b) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593. (c) Buon, C.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 701. (d) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.
- (21) (a) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (c) Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 7875. (d) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757.
- (22) (a) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *Chem. Commun.* **2006**, 4137. (b) Tang, Z.-Y.; Spiniella, S.; Hu, Q.-S. *Tetrahedron Lett.* **2006**, *47*, 2427. (c) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215. (d) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett.* **2005**, *46*, 4261. (e) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (f) Campbell, I. B.; Guo, J.; Jones, E.; Steel, P. G. *Org. Biomol. Chem.* **2004**, *2*, 2725. (g) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (h) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3190. (i) Wu, J.; Wang, L.; Fathi, R.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 4395. (j) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (k) Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969. (l) Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321. (m) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060.
- (23) (a) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457. (b) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (d) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *39*, 8739. (e) Hayashi, T.; Fujiwara, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001. (f) Hayashi, T.; Katsuro, Y.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4449.
- (24) (a) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. (b) Lo, Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360. (c) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673.
- (25) (a) Klapars, A.; Campos, K. R.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
- (26) (a) Hansen, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585. (b) Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Chou-Hong, T.; Thiruvengadam, K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573.

## Scheme 2



conditions,<sup>22b,e,j,l,m</sup> similar Ni(0)-promoted Heck couplings with electron deficient alkenes are less efficient necessitating high reaction temperatures (ca. 150 °C) due to a slow  $\beta$ -elimination step of the alkyl Ni(II) intermediate.<sup>27</sup>

In an earlier communication, we reported the Heck coupling of nonactivated cyclic alkenyl tosylates with a variety of electron deficient olefins (Scheme 1).<sup>28</sup> We established that these vinylations could effectively be promoted by the combination of PdCl<sub>2</sub>(COD) and P(*t*-Bu)<sub>3</sub> with Cy<sub>2</sub>NMe as a base in DMF, conditions which were similar to those developed by Fu and co-workers for the Heck coupling of aryl chlorides.<sup>5b,d</sup> However, for successful C–C bond formation, the addition of 1 equiv of LiCl was obligatory.

This catalytic system was also extended to the Heck reactions of several simple acyclic vinyl tosylates and two phosphates.<sup>29</sup> Unexpectedly, in the case of alkenes possessing a large C1-substituent represented by a *tert*-butyl or a trimethylsilyl group, coupling products resulting from an effective 1,2-migration were obtained in yields attaining 95% (Scheme 2).<sup>28,30</sup> 1,2-Migrations are quite rare for Pd(0)-catalyzed coupling reactions having only briefly been reported in two other occasions. Hartwig and co-workers described a single case of this rearrangement in the Pd(0)-catalyzed Kumada coupling of alkenyl tosylates using Josiphos-type ligands,<sup>23b</sup> whereas the group of Miyaura observed 1,2-migration as a biproduct in the Pd-catalyzed synthesis of vinyl boronic esters.<sup>31</sup>

To explain the 1,2-migration observed for these Heck reactions, we proposed that a tricoordinated T-shaped Pd(II) complex **A** formed after the oxidative addition was the key to the rearrangements observed with the 1-*tert*-butyl vinyl tosylate

or phosphate (Figure 1). Such an arrangement, which has earlier been reported for Pd(II) complexes possessing bulky phosphine ligands, deviates from the normal tetracoordinated square planar complexes by possessing a free coordination site.<sup>32</sup> Hence,  $\beta$ -hydride elimination is facilitated generating the *tert*-butyl acetylene hydride palladium(II) complex **B**, whereafter rotation of the acetylene group and hydropalladation then afford the alternative tricoordinated T-shaped palladium species **C**. DFT calculations performed with these intermediates of the catalytic cycle suggested that the highest barrier for isomerization between **A** and **C** was only 62 kJ/mol implying that migration is rapid under the reaction conditions used.<sup>28</sup> On the other hand, carbopalladation represented the rate determining step where insertion was found to be more favored for intermediate **C** than **A**.

Ideally, catalysts which can either effectively promote or prevent the 1,2-migration using alkyl or aryl vinyl phosphates as substrates in the Heck reaction would be of high interest. In this paper, we report full studies on the achievement of one of these goals with the identification of a catalytic system consisting of a Pd(0) catalyst with an alternative, sterically hindered, and electron rich phosphine which promotes the Heck coupling *without migration* between a wide variety of aryl and alkyl vinyl phosphates with olefins in good yields. Furthermore, we have performed additional experiments to examine the scope and limitations of the 1,2-migration in the Heck coupling with vinyl phosphates and to further understand the factors which control the 1,2-migration. Our work demonstrates that with certain reactants the Heck reaction can be promoted with or without the 1,2-migration through the proper choice of the catalyst composition and additive. This work extends the utility of this valuable carbon–carbon bond forming reaction.

## Results and Discussion

**Heck Coupling Conditions without 1,2-Migration.** We hypothesized in our earlier work that a key factor to the observation of 1,2-migrations in the Heck coupling of alkenyl tosylates and phosphates was the formation of a tricoordinated Pd(II) complex after the oxidative addition step thereby providing a free site on palladium for the ensuing  $\beta$ -elimination step.

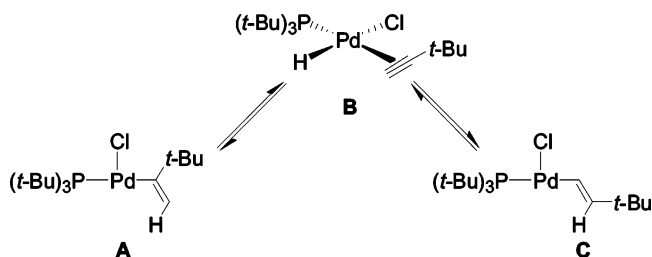
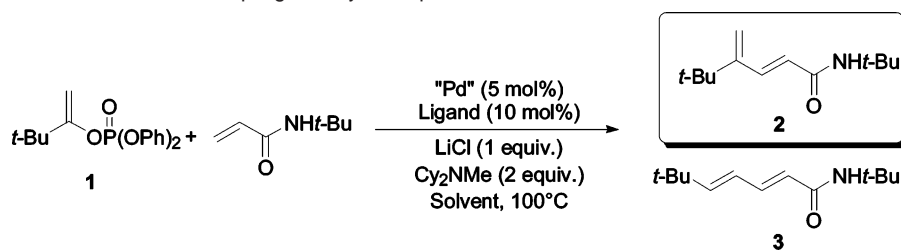


Figure 1. Proposed mechanism for the 1,2-migration.

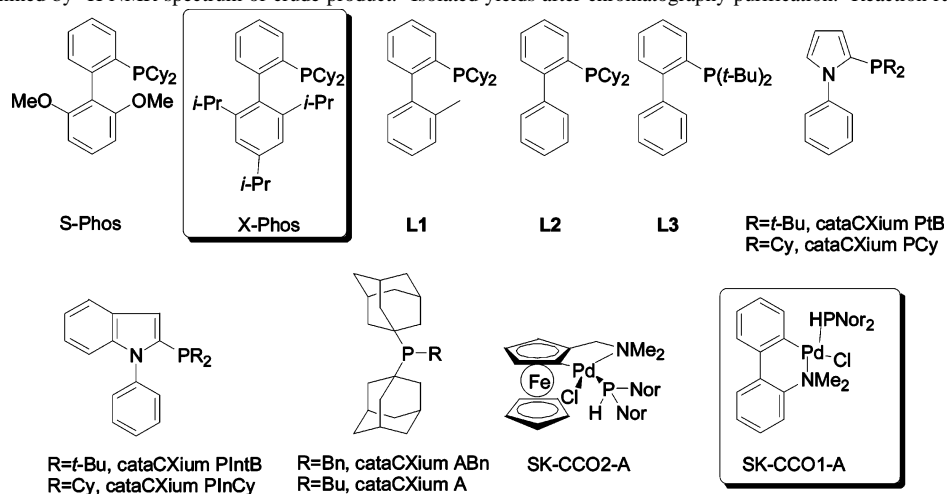
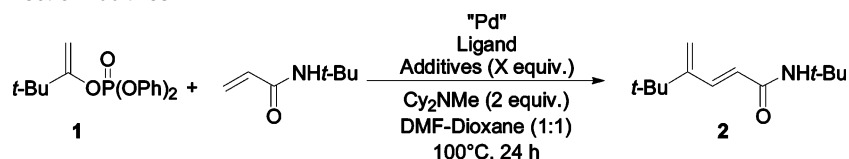
- (27) (a) Ma, S.; Wang, H.; Gao, K.; Zhao, F. *J. Mol. Catal. A: Chem.* **2006**, *248*, 17. (b) Inamoto, K.; Kuroda, J.-I.; Danjo, T.; Sakamoto, T. *Synlett* **2005**, 10, 1624. (c) Houdayer, A.; Schneider, R.; Billaud, D.; Ghanbaja, J.; Lambert, J. *Synth. Met.* **2005**, *151*, 165. (d) Lin, B.-L.; Liu, L.; Fu, Y.; Luo, S. W.; Chen, Q.; Guo, Q. *Z. Organometallics* **2004**, *23*, 2114. (e) Bhanage, B. M.; Zhao, F.; Shirai, M.; Arai, M. *Catal. Lett.* **1998**, *54*, 195. (f) Iyer, S.; Ramesh, C.; Ramani, A. *Tetrahedron Lett.* **1997**, *38*, 8533. (g) Kelkar, A. A. *Catal. Lett.* **1994**, *29*, 69.
- (28) Hansen, A. L.; Ebran, J. P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.
- (29) For the only other Pd-catalyzed Heck reaction with a vinyl phosphate, see: Coe, J. W. *Org. Lett.* **2000**, *2*, 4205.
- (30) For examples of other migrations in Pd(0)-catalyzed reactions, see: (a) Fayol, A.; Fang, Y. Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (b) Lautens, M.; Jafarpour, F. *Org. Lett.* **2006**, *8*, 3601. (c) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340. (d) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694. (e) Mota, A. J.; Dedieu, A. *Organometallics* **2006**, *25*, 3130. (f) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (g) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512. (h) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701. (i) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (j) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (k) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (l) Karig, G.; Moon, M. T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (m) Lautens, M.; Piguél, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (n) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (o) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421.
- (31) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.



**Table 1.** Optimization Studies in the Heck Coupling of Vinyl Phosphates

entry	"Pd"/ligand	solvent	conversion <sup>a</sup> (yield) <sup>b</sup>	2:3
1	PdCl <sub>2</sub> (COD), S-Phos	DMF	33%	>99:1
2	PdCl <sub>2</sub> (COD), X-Phos	DMF	48% (37%)	>99:1
3	PdCl <sub>2</sub> (COD), L1	DMF	<5%	
4	PdCl <sub>2</sub> (COD), L2	DMF	<5%	
5	PdCl <sub>2</sub> (COD), L3	DMF	38%	>99:1
6	PdCl <sub>2</sub> (COD), cataXCium PtB	DMF	22%	
7	PdCl <sub>2</sub> (COD), cataXCium Pcy	DMF	<5%	
8	PdCl <sub>2</sub> (COD), cataXCium PintB	DMF	<5%	
9	PdCl <sub>2</sub> (COD), cataXCium PintCy	DMF	<5%	
10	SK-CCO1-A	DMF	47%	>99:1
11	SK-CCO2-A	DMF	13%	>99:1
12	PdCl <sub>2</sub> (COD), X-Phos <sup>c</sup>	DMF	21%	54/46
13	PdCl <sub>2</sub> (COD), X-Phos	Dioxane	23%	>99:1
14	PdCl <sub>2</sub> (COD), X-Phos	DMF–Dioxane <sup>d</sup>	56% (45%)	>99:1

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product. <sup>b</sup> Isolated yields after chromatography purification. <sup>c</sup> Reaction run at 140 °C. <sup>d</sup> 1:1 ratio.

**Table 2.** Studies on the Effect of Additives

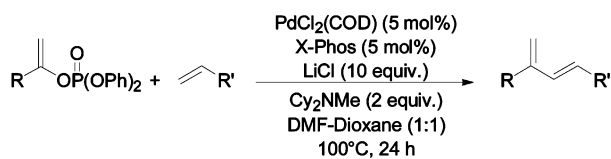
entry	catalytic system	additives (X equiv)	conversion <sup>a</sup> (yield) <sup>b</sup>
1	PdCl <sub>2</sub> (COD) (2.5%), X-Phos (5%)	LiCl (2)	70%
2	PdCl <sub>2</sub> (COD) (2.5%), X-Phos (5%)	LiCl (4)	86%
3	PdCl <sub>2</sub> (COD) (2.5%), X-Phos (5%)	LiCl (10)	99%
4	PdCl <sub>2</sub> (COD) (2.5%) <sup>c</sup>	LiCl (10)	10%
5	PdCl <sub>2</sub> (COD) (2.5%), X-Phos (5%)	NaCl (10)	<5%
6	PdCl <sub>2</sub> (COD) (2.5%), X-Phos (2.5%)	LiCl (10)	77%
7	PdCl <sub>2</sub> (COD) (5%), X-Phos (5%)	LiCl (10)	100% (91%)
8	SK-CCO1-A (5%)	LiCl (10)	90%

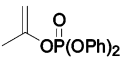
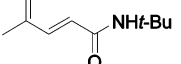
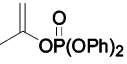
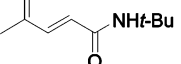
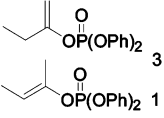
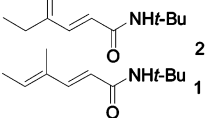
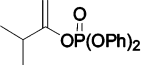
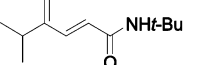
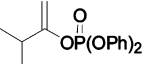
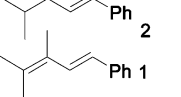
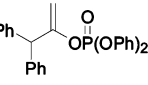
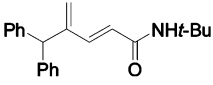
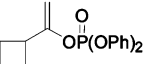
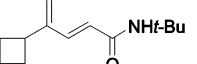
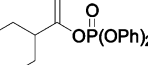
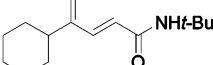
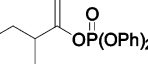
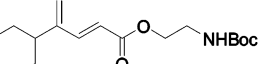
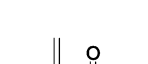
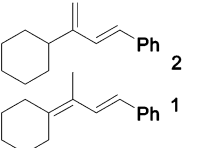
<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product. <sup>b</sup> Isolated yield after chromatography purification. <sup>c</sup> Only DMF was used as solvent.

This latter step could potentially be hindered through the use of a bidentate type ligand which prevents interaction of the metal center with the vinylic hydrogen. To this end, experiments were

conducted to identify suitable reaction conditions for the coupling of 1-*tert*-butylvinyl *O,O*-diphenyl phosphate (**1**) with *N-tert*-butyl acrylamide examining a wide range of phosphine

**Table 3.** Heck Coupling of Primary and Secondary Alkenyl Vinyl Phosphates without Migration



Entry	Vinyl Phosphate	Product	Yield <sup>a</sup> (conversion) <sup>b</sup>
1			45% (57%)
2			65% (94%) <sup>c</sup>
3			80% (82%)
4			83% (92%)
5			71% (100%)
6			83% (90%)
7			68% (100%)
8			70% (90%)
9			47% (100%)
10			67% (100%)

<sup>a</sup> Isolated yield after chromatography purification. <sup>b</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product. <sup>c</sup> Reaction after 72 h.

ligands in combination with the palladium source, PdCl<sub>2</sub>(COD) (Table 1). The alkenyl phosphates used in these studies were easily prepared from the corresponding ketones via an initial deprotonation step with LHMDS in THF at -78 °C followed by the addition of a slight excess of diphenyl phosphoryl chloride.<sup>23b,28</sup> As the cost of the phosphorylation reagent is

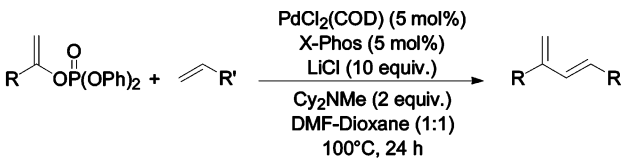
considerably less than that of tosyl anhydride required for the preparation of the corresponding vinyl tosylates, the following study was continued primarily with the alkenyl phosphates.<sup>33</sup>

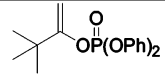
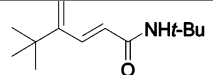
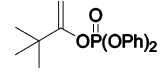
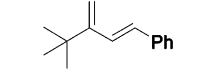
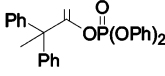
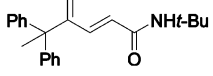
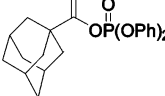
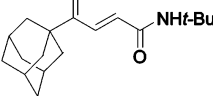
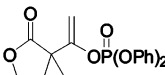
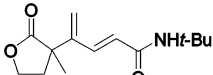
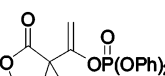
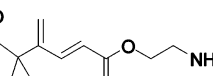
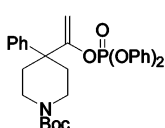
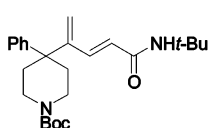
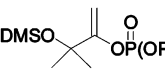
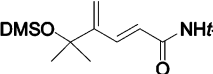
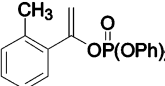
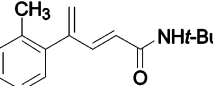
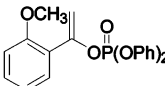
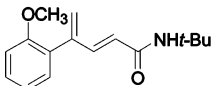
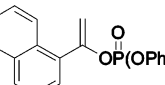
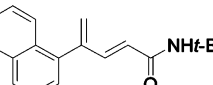
Preliminary screenings were performed with a variety of commercially available bidentate ligands including dppe, dppp,

(32) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184.

(33) Aldrich prices from the 2007 catalogue on reagent grade compounds in euro/mol: tosyl anhydride = 1781 euro (50 g package of >95% purity), diphenyl phosphoryl chloride = 135 euro (100 g package of 96% purity).

Table 4. Heck Coupling of Quaternary Alkyl and Aryl Vinyl Phosphates without Migration



Entry	Vinyl Phosphate	Product	Yield <sup>a</sup> (conversion) <sup>b</sup>
1			91% (100%)
2			60% (100%)
3			63% (100%)
4			81% (100%)
5			62% (76%)
6			49% (100%)
7			93% (100%)
8			57% (100%)
9			80% (95%)
10			89% (100%)
11			79% (92%)

<sup>a</sup> Isolated yield after chromatography purification. <sup>b</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product.

dppb, dppf, b7bpf, BINAP, and the Josiphos class of ligands (results not shown). All reactions were run for 24 h in DMF at 100 °C with a catalyst loading of 5 mol %, dicyclohexylmethylamine (Cy<sub>2</sub>NMe) as the base, and 1 equiv of LiCl in order to avoid the presence of the Pd(II) cationic species. Whereas low conversion was observed in some cases (<10%), it was interesting to note that only the Heck product without

migration could be observed. The use of the tertiary amine base Cy<sub>2</sub>NMe proved to be the most adequate compared to other organic bases such as DIPEA or NEt<sub>3</sub> and inorganic bases such as Cs<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> (results not shown).

More promising results were obtained upon examining a variety of the commercially available dialkylbiarylphosphines introduced by Buchwald<sup>34</sup> (Table 1, entries 1–5), as such

**Table 5.** Heck Coupling of 1,2-disubstituted Alkyl Vinyl Phosphates without Migration

Entry	Vinyl Phosphate	Product	Yield <sup>a</sup> (ratio) <sup>b</sup>
1			88% (2:1)
2			68% (3.6:2.4:1) <sup>c</sup>
3			76% (3:1)
4			58% (4:1)
5			80% (7:3) <sup>d</sup>

<sup>a</sup> Isolated yield after chromatography purification. <sup>b</sup> Ratio of isomers determined by <sup>1</sup>H NMR spectrum of crude product. <sup>c</sup> See Supporting Information. <sup>d</sup> Configuration of the major isomer was determined by single-crystal X-ray analysis to be the *Z*-isomer (see Supporting Information).

ligands are both electron rich and, as demonstrated with *S*-Phos and *X*-Phos, display an ability to coordinate to the metal center via interaction with the biaryl unit.<sup>35</sup> *X*-Phos, *S*-Phos, and **L3** promoted the Heck coupling and importantly without migration (entries 1 and 2), although conversions were moderate.<sup>36,37</sup> As in the earlier reactions with *P*(*t*-Bu)<sub>3</sub>, the addition of LiCl was mandatory for any conversion in these vinylation reactions. Of the range of other catalyst systems tested (entries 6–11), only the Solvias palladium(II) catalyst (SK-CCO1-A, entry 10)<sup>38</sup>

demonstrated comparable reactivity to that of the combination of PdCl<sub>2</sub>(COD) and *X*-Phos with the sole formation of the diene **2**.

Further optimization studies performed with *X*-Phos (Table 1, entries 12–14) revealed that the use of the solvent mixture DMF/dioxane (1:1) led to a slight improvement in the conversion of **1**. However, as illustrated in Table 2 (entries 1–3), a remarkable positive effect was observed upon increasing the number of equivalents of LiCl to 10 equiv resulting in a quantitative conversion. Furthermore, a catalyst loading of 5 mol % with a Pd/ligand ratio of 1:1 furnished the most reliable system in the subsequent studies. Under these conditions, a satisfactory 91% isolated yield of the Heck product **2** was obtained (entry 7).<sup>39</sup> Interestingly, the catalyst SK-CCO1-A also displayed improved catalytic behavior when subjected to excess LiCl (entry 8) leading to a 90% conversion of the vinyl phosphate **1**.

We then proceeded to examine the generality of these reaction conditions with a variety of primary and secondary alkyl vinyl phosphates and electron deficient alkenes. As depicted in Table 3, the normal Heck product could be isolated in all cases in

- (34) (a) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484. (b) Burgos, C. H.; Barder, T.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321. (c) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (d) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6173. (e) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523 and references cited therein.
- (35) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Barder, T. E. *J. Am. Chem. Soc.* **2005**, *127*, 898. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (d) Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714.
- (36) For two examples of successful Heck reactions exploiting *X*-Phos as ligand, see: (a) Cameron, M.; Foster, B. S.; Lynch, J. E.; Shi, Y.-J.; Dolling, U.-H. *Org. Process Res. Dev.* **2006**, *10*, 398. (b) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826.
- (37) (a) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, T.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237. (b) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983.
- (38) (a) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583. (b) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668.

- (39) Possible explanations for the LiCl effect in these reactions could be (a) an increase in the ionic strength of the solvent facilitating the oxidative additions step in much the same manner as with Heck reactions performed in ionic liquids (refs 10a, 11b, 40) or under ligandless conditions as reported by Jeffery and others (ref 41), or (b) the greater number of equivalents of LiCl may augment the concentration of a more reactive anionic Pd(0) complex in equilibrium with its neutral species (refs 11h, 12a, 15c,e, 42, 43).

Table 6. Heck Coupling of Quaternary Alkyl Vinyl Phosphates with 1,2-Migration

Entry	Vinyl phosphate	Conversion <sup>a</sup>	Yield <sup>b</sup> (migrat.:normal) <sup>c</sup>	Product
1		59%	50% (93:7)	
2		100%	73% (9:1)	
3		84%	75% (9:1)	
4		44%	36% (>99:1)	
5		100%	81% (2:5)	
6		n.r. <sup>d</sup>	-	-
7		n.r. <sup>d</sup>	-	-

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product. <sup>b</sup> Isolated yield after chromatography purification. <sup>c</sup> Ratio of isomers determined by <sup>1</sup>H NMR spectrum of crude product. <sup>d</sup> No reaction.

moderate to good yields. Reactions were stopped after 24 h for the sake of comparison of substrate reactivity, but longer reaction times could nevertheless be applied providing evidence for the high stability of the catalytic system. For example, the 1-methyl vinyl phosphate exhibited a mediocre reactivity (entry 1) compared to the other phosphates but, by increasing the reaction time to 72 h, furnished a 65% yield of the diene system (entry 2). Alkenyl phosphates carrying other alkyl groups including rings at the C1-position proved to be sufficiently reactive with *N*-*tert*-butyl acrylamide (entries 3, 4, and 6–8) under these catalytic conditions. Partial isomerization of the unsaturation in the product was observed, however, in coupling reactions performed with styrene (entries 5 and 10).

A series of vinyl phosphates possessing a C1-quaternary carbon were examined leading to the required dienes upon Heck

reaction with acrylamide, styrene, or acrylate in yields ranging from 49 to 93% (Table 4, entries 1–8). Both simple and more functionalized C1-substituted vinyl phosphates coupled smoothly with excellent regioselectivity in favor of the nonmigrated products. Aryl vinyl phosphates were also suitable for these coupling reactions as revealed with the three examples in entries 9–11, generating 3-aryl dienes in good yields.

To complete this initial study, a few examples of Heck reactions between 1,2-disubstituted vinyl phosphates and *N*-*tert*-butyl acrylamide were tested as illustrated in Table 5. Although the coupling yields were in general good, in most cases some scrambling of the stereochemistry at the terminal alkene position was observed (entries 1–5). As exemplified with the *N*-vinyl oxazolidinone derivative in entry 5, its coupling furnished the disubstituted pentadienamides in 80% yield as a 7:3 mixture of



Table 7. Heck Coupling of Aryl Vinyl Phosphates with 1,2-Migration

Entry	Vinyl phosphate	Conversion <sup>a</sup>	Yield <sup>b</sup> (migrat.:normal) <sup>c</sup>	Product
1		100%	95% (10:1)	
2		90%	80% (1:1) <sup>d</sup>	
3		100%	96% (3:1)	
4		100%	91% (1:2)	
5		100%	74% (>99:1)	
6		100%	81% (<1:99)	

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectrum of crude product. <sup>b</sup> Isolated yield after chromatography purification. <sup>c</sup> Ratio of isomers determined by <sup>1</sup>H NMR spectrum of crude product. <sup>d</sup> Reaction carried out at 60 °C.

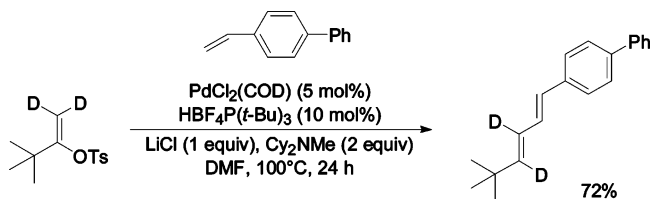
stereoisomers. The stereochemical assignments of the products were established by an X-ray structural analysis of the major product (see Supporting Information). Either thermal isomerization or readdition of the Pd–H intermediate and subsequent elimination may account for the mixture of stereoisomers obtained in these cases.

**Scope and Limitations of the Heck Coupling with 1,2-Migration.** With the identification of suitable reaction conditions which promote Heck couplings with alkenyl phosphates, we then proceeded to examine the scope and limitation of similar coupling reactions under conditions which promote 1,2-migration as previously published with the 1-*tert*-butyl vinyl phosphate and the equivalent tosylate.<sup>28</sup> However, the vinyl phosphates bearing a C1-alkyl substituent with an  $\alpha$ -hydrogen as illustrated in Table 3, entries 1–6, proved surprisingly unreactive to the reaction conditions exploiting the PdCl<sub>2</sub>(COD)/P(*t*-Bu)<sub>3</sub>/Cy<sub>2</sub>-NMe system, also illustrating the high stability of these alkenyl phosphates.<sup>40–44</sup>

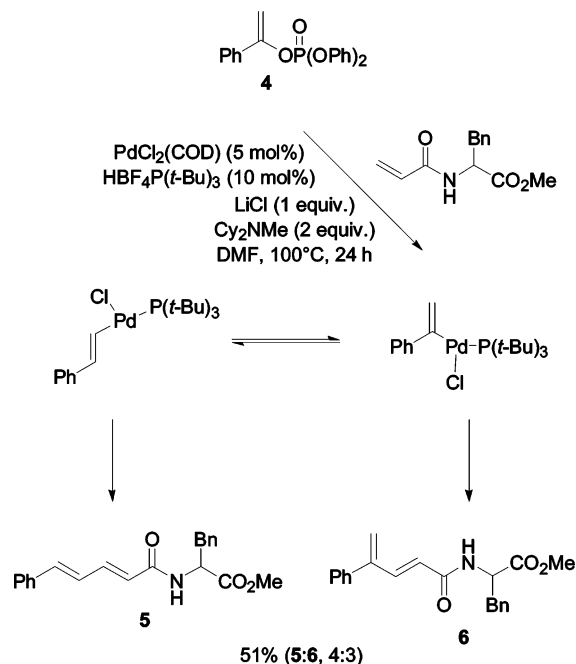
Even the 1,2-disubstituted vinyl phosphate illustrated in Table 5, entry 1, failed to undergo a coupling reaction with the acrylamide. On the other hand, similar reactions with the corresponding tosylate resulted only in the disappearance of the

- (40) (a) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 3298. (b) Xiao, J.-C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2004**, *6*, 3845. (c) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243.
- (41) (a) Pryjomska-Ray, I.; Trzeciak, A. M.; Ziólkowski, J. J. *J. Mol. Cat. A: Chem.* **2006**, *257*, 3. (b) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, *14*, 1559. (c) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528. (d) Kogan, V.; Aizenshtat, Z.; Popovits-Biro, R.; Neumann, R. *Org. Lett.* **2002**, *4*, 3529. (e) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (f) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (g) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113. (h) Jeffery, T.; Galland, J.-C. *Tetrahedron Lett.* **1994**, *35*, 4103. (i) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
- (42) (a) Camp, D.; Matthews, C. F.; Neville, S. T.; Rounes, M.; Scott, R. W.; Truong, Y. *Org. Process Res. Dev.* **2006**, *10*, 814. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
- (43) Interestingly, in the synthesis of a GABA  $\alpha$ 2/3 agonist, Cameron and coworkers observed a positive effect on the addition of ammonium salts in a Heck coupling exploiting Pd(OAc)<sub>2</sub> and X-phos as the catalytic system (see ref 36a).

Scheme 3



Scheme 4



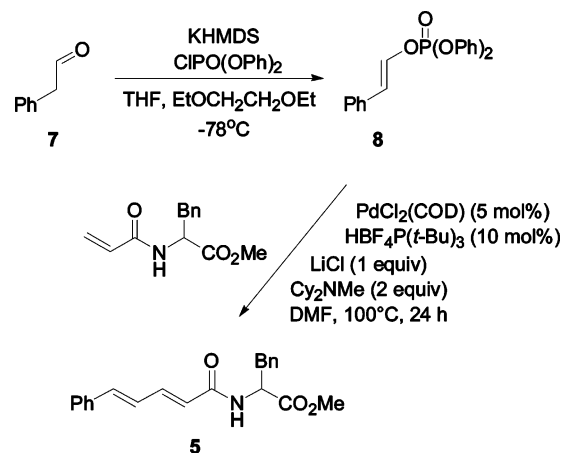
starting material without the formation of either of the two desired dienes.<sup>45</sup> Remarkably, this same substrate was reported by Hartwig and co-workers to undergo a 1,2-migration in the Kumada cross coupling with *p*-tolyl magnesium bromide catalyzed by a Pd(0)/Josiphos complex.<sup>23b</sup> Although this latter reaction was performed in toluene, there is the possibility that an alternative mechanism may be operating in this isomerization observed for the Kumada coupling.

Greater success was achieved studying the scope of alkenyl phosphates possessing an alkyl quaternary carbon at C1. As depicted in Table 6, the substrates in entries 1 to 5 proved adaptable to these coupling conditions producing the Heck products in 36–81% yield and with the exception of entry 5 in favor of the isomerized diene with regioselectivities  $\geq 9:1$ . Presumably, the low level of migration in the case of the lactone (entry 5) can be explained by an intramolecular chelation of the carbonyl oxygen with the metal center after the oxidative addition step, thereby blocking the free site for the subsequent  $\beta$ -elimination step. The rate of these reactions nevertheless

(44) Possibly the alkenyl phosphates bearing a C1-quaternary carbon possess longer and hence weaker C1–O bonds due to unfavorable steric interactions between the phosphate group and the C1-substituent compared to C1-alkyl substituents with an  $\alpha$ -proton, which facilitates their entry into the first step of the catalytic cycle.

(45) A simple base induced elimination reaction of the vinyl tosylate involving the  $\alpha$ -proton of the alkyl side chain would lead to the formation of a volatile trisubstituted allene. Alternatively, if the oxidative addition step is more facile with vinyl tosylates than with the phosphates, the generated alkenyl-Pd(II) intermediate could undergo a  $\beta$ -hydride elimination step again involving the same alkyl sidechain with the formation of an allene, which competes successfully with either the insertion step or the elimination of the olefin hydrogen.

Scheme 5



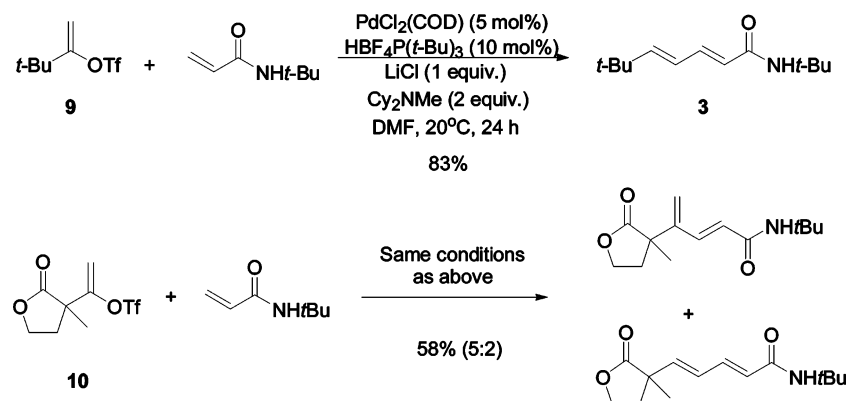
appeared to be influenced by the substituents on the alkenyl phosphates as a low conversion was observed for the substrate possessing a 1,1-diphenylethyl substituent, whereas no reactivity was detected with the reactants in entries 6 and 7. This is in contrast to similar Heck couplings applying X-Phos as the ligand where acceptable yields of the diene products without migration were noted (Table 4, entries 3 and 8).

Finally, we investigated the reactivity of C1-aryl substituted vinyl phosphates toward the 1,2-migration under the Heck coupling conditions,  $\text{PdCl}_2(\text{COD})/\text{P}(\text{t-Bu})_3/\text{Cy}_2\text{NMe}$  in DMF at  $100^\circ\text{C}$ , with *N-tert*-butyl acrylamide. It was quickly discovered that substrates bearing an *ortho*-substituent on the aromatic ring led to both cleaner reactions and higher yields of the desired coupling products (Table 7). In the absence of these substituents, typically either complex product mixtures were furnished, which potentially originate from Diels–Alder cycloadditions involving migrated and nonmigrated dienes products, or degradation of the starting material was detected. As exemplified in entry 1, the C1-*o*-tolyl derivative couples with the acrylamide in an excellent yield of 95% with a good regioselectivity in favor of the 1,2-migration (10:1). Whereas good yields were also obtained in entries 2–4, only modest results in the 1,2-migration were noted. On the other hand, the vinyl phosphate bearing a C1-anthracenyl unit led to complete migration upon coupling (entry 5). Interestingly, in the case of the perfluorophenyl vinyl phosphate, the reaction took place without rearrangement, providing the normal coupling product in an 81% yield (entry 6). Electronic factors could be at play in this special case. In contrast, the low selectivity observed for the *ortho*-methoxy- and dimethoxyphenyl substrates may be explained by an intramolecular chelation of the divalent metal center with one of the methoxy groups, particularly as a high degree of 1,2-migration was noted in the coupling product from the *o*-tolyl vinyl phosphate. The coupling reaction with the dimethoxyphenyl vinyl phosphate nevertheless favored the 1,2-migration with respect to the monomethoxy substrate, possibly because of the greater steric bulk of the di-*ortho*-substituted aryl ring.

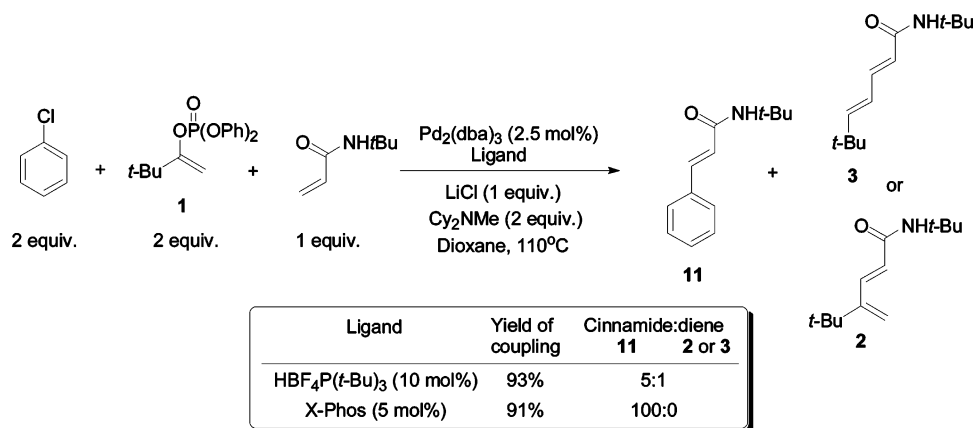
#### Further Studies on the Heck Coupling with 1,2-Migration.

In our earlier work, both DFT calculations and a deuterium labeling experiment provided support for the 1,2-migration step proceeding through a  $\beta$ -hydride elimination step of a tricoordinated Pd(II) species generated after the oxidative addition step (Figure 1 and Scheme 3).<sup>28</sup>

Scheme 6



Scheme 7



To further probe the proposed mechanism, we turned our attention to a previous observation in the Heck coupling of 1-phenyl vinyl phosphate **4** (Scheme 4). Under the coupling conditions which promote 1,2-migration, the reaction of **4** with the acrylamide of phenylalanine methyl ester led to the formation of an approximately 1:1 mixture of regioisomeric products **5** and **6** in a 51% yield. As a rapid equilibrium between the two isomeric Pd(II) alkene species was supported by DFT calculations, the above experiment suggested that both insertion steps for the substrate **4** proceed at approximately the same rates in contrast to similar experiments with the *tert*-butyl vinyl phosphate **1**. If this is correct, then the same product distribution should be anticipated starting from the isomeric 2-phenyl vinyl phosphate.

To investigate this point, the *trans*-vinyl phosphate **8** was prepared from aldehyde **7** via deprotonation with potassium hexamethyldisilazide and subsequent reaction of the potassium enolate intermediate with diphenyl phosphoryl chloride (Scheme 5). Subjecting the phosphate **8** to the same coupling conditions and the identical acrylamide (0.75 equiv) led to the exclusive formation of one Heck product identified as the diene **5** according to the crude  $^1\text{H}$  NMR spectrum. This unexpected result evidently does not provide support for the  $\beta$ -hydride elimination mechanism, unless the equilibration between the two intermediate Pd(II) alkene species is not as rapid as the case for the *tert*-butyl vinyl phosphate or tosylate. The same reactivity was observed for the analogous vinyl tosylate prepared in the same fashion as the alkenyl phosphate. Even the reaction of  $\beta$ -bromostyrene with *N-tert*-butyl acrylamide afforded solely the

nonmigrated product in high yield when performed at 100 °C. Interestingly, no reaction was observed at room temperature.

Additional work was also carried out to investigate the effect of the reaction temperature on the ratio of isomeric products. Here our attention was focused on the use of the analogous vinyl triflates due to their greater reactivity toward oxidative addition which therefore permits the use of lower reaction temperatures. With the same catalytic system,  $\text{PdCl}_2(\text{COD})/\text{P}(\text{t-Bu})_3/\text{Cy}_2\text{NMe}$  in DMF, the coupling of *tert*-butyl vinyl triflate **9** with *N-tert*-butyl acrylamide proceeded efficiently at 20 °C providing a single diene product **3** in an 83% yield arising from a 1,2-migration (Scheme 6). Similarly, in the Heck coupling of the  $\gamma$ -lactone vinyl triflate **10**, a rearranged/nonrearranged ratio of 2:5 was observed in the product, which corresponds to the same ratio obtained for the analogous vinyl phosphate compound (Table 6, entry 5).

With the ability of the vinyl triflates to undergo Heck couplings with 1,2-migration at lower temperatures, it became interesting to examine alkenyl triflates bearing alkyl substituents with an  $\alpha$ -hydrogen. However, it became quickly clear that the triflates or their nonaflate counterparts are not compatible to the reaction conditions providing no coupling products in attempts to couple with the *N-tert*-butyl acrylamide. Even in the absence of the palladium source, the starting vinyl triflates or nonaflates decomposed suggesting that a base or chloride induced elimination reaction may be taking place. Similar results were obtained in Heck coupling reactions performed with X-Phos as the ligand, where the corresponding vinyl phosphates function admirably.

Finally, competition experiments were performed in order to compare the reactivities of chlorobenzene with the *tert*-butyl vinyl diphenyl phosphate **1**. These experiments were performed using 2 equiv of both the aryl halide and **1** and 1 equiv of the *N*-*tert*-butyl acrylamide employing slightly modified conditions to those previously reported by Littke and Fu with Pd<sub>2</sub>(dba)<sub>3</sub>/Cy<sub>2</sub>NMe/LiCl in dioxane at 110 °C (Scheme 7).<sup>5b</sup> Interestingly, in both reactions performed using either P(*t*-Bu)<sub>3</sub> or X-Phos as the ligand system the phenyl chloride reacted preferentially leading to the formation of the cinnamide product **11**. In addition, in all the coupling reactions performed with the vinyl diphenyl phosphates, no products were observed from oxidative addition in the O-phenyl bond. This result suggests that for Heck reactions aryl chloride derivatives are considerably more reactive than either the vinyl or phenyl phosphates where the latter may be placed on the far right side of the scale of reactivities of various groups involved in the oxidative insertion step (I > OTf ≥ Br > Cl > OP(O)(OPh)<sub>2</sub>). Such information is undoubtedly important for predicting reactivities in coupling reactions with substrates possessing multiple reactive sites.

## Conclusions

In summary, we have identified suitable reaction conditions which promote the Pd(0)-catalyzed Heck coupling of nonactivated vinyl phosphates with electron deficient alkenes providing an entry to diene products from simple and readily accessible starting materials. In contrast to our earlier work exploiting P(*t*-Bu)<sub>3</sub> as ligand, the use of an alternative bulky phosphine such as Buchwald's X-Phos effectively promoted the coupling with a wide range of alkenyl phosphates in the presence of excess lithium chloride. Notably 1,2-migration of the alkenyl palladium-(II) intermediate was suppressed in these Heck couplings. Further studies were also carried out with the catalytic system which encourages isomerization in order to determine the extent of reactants which may participate in such reactions. Alkenyl phosphates with C1-substituents devoid of an α-hydrogen in the C1-position displayed an ability to participate in an effective coupling. The extent of the 1,2-migration was nevertheless dependent on the C1-substituent where the best results were observed with an alkyl quaternary carbon at C1. Although the usefulness of this isomerization process is limited to a small range of alkyl vinyl phosphates, it is interesting with this class of substrates that synthesis of either the migrated or nonmigrated Heck products may be executed through the selection of the phosphine ligand. Finally, competition experiments performed with a palladium catalyst possessing either X-Phos or P(*t*-Bu)<sub>3</sub> as ligand revealed that an unactivated aryl chloride is more reactive than *tert*-butyl vinyl phosphate in their Heck coupling to arylamides. These results reveal a preference for oxidative addition of the palladium(0) catalyst into the aryl chloride bond rather than the C–O bond of the alkenyl phosphate.

Further studies are now underway to examine whether these Heck couplings may be extended to include aryl tosylates and phosphates as well. Preliminary results performed in these laboratories suggest that the catalyst systems applied in this work with alkenyl phosphates and tosylates are less efficient for catalyzing these C–C bond formations with such substrates, and hence further optimization studies are required. This work will be reported in due course.

## Experimental Section

**General Methods.** Solvents were dried according to standard procedures. Reactions were monitored by thin-layer chromatography (TLC), and flash chromatography was performed on silica gel 60 (230–400 mesh). The chemical shifts of the NMR spectra are reported in ppm relative to the solvent residual peak.<sup>46</sup> MS spectra were recorded on an LC TOF (ES) apparatus. All Heck couplings were carried out in 7.0 mL sample vials with a Teflon sealed screwcap in a glovebox under an argon atmosphere. All purchased chemicals were used as received without further purification. The vinyl phosphates were synthesized according to methods previously reported.<sup>23b,28</sup>

**(E)-4-Adamantyl-*N*-*tert*-butyl Penta-2,4-dienamide (Table 4, Entry 4). General Procedure for the Heck Couplings of Nonactivated Vinyl Phosphates without 1,2-Migration.** Lithium chloride (169.6 mg, 4.00 mmol), X-Phos (9.6 mg, 0.02 mmol), 1-adamantyl vinyl diphenylphosphate (246.3 mg, 0.60 mmol), *N*-*tert*-butyl acrylamide (50.9 mg, 0.40 mmol), Cy<sub>2</sub>NMe (170 μL, 0.80 mmol), and PdCl<sub>2</sub>(COD) (5.7 mg, 0.02 mmol) dissolved in a 1:1 DMF–Dioxane mixture (3 mL) were reacted for 24 h at 100 °C. The crude product was purified by flash chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent. This afforded 93 mg of the title compound (81% yield) as a colorless solid. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ (ppm) 7.35 (d, 1H, *J* = 15.4 Hz), 6.10 (d, 1H, *J* = 15.4 Hz), 5.95 (bs, 1H, NH), 5.16 (t, 1H, *J* = 1.2 Hz), 4.76 (d, 1H, *J* = 1.2 Hz), 1.80 (m, 3H), 1.55 (m, 9H), 1.50 (m, 3H), 1.24 (s, 9H). <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) 165.0, 155.4, 139.0, 125.0, 109.9, 51.0, 41.2, 37.2, 36.8, 28.9, 28.6. HRMS C<sub>19</sub>H<sub>29</sub>NO [M + Na<sup>+</sup>]: 310.2147. Found: 310.2153.

**(2E, 4E)-6,6-Adamantyl-*N*-*tert*-butyl Hepta-2,4-dienamide (Table 6, Entry 2). General Procedure for the Heck Couplings of Nonactivated Vinyl Phosphates with 1,2-Migration.** Lithium chloride (17.4 mg, 0.40 mmol), HBF<sub>4</sub>P(*t*-Bu)<sub>3</sub> (11.6 mg, 0.04 mmol), 1-adamantyl vinyl diphenylphosphate (246.3 mg, 0.60 mmol), *N*-*tert*-butyl acrylamide (50.9 mg, 0.40 mmol), Cy<sub>2</sub>NMe (170 μL, 0.80 mmol), and PdCl<sub>2</sub>(COD) (5.7 mg, 0.02 mmol) dissolved in DMF (3 mL) were reacted for 24 h at 100 °C. The crude product was purified by flash chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent. This afforded 83.3 mg of the title compound (73% yield) as a colorless solid with an overall rearranged/nonrearranged ratio >9:1. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>–CD<sub>3</sub>CN (1:1)) δ (ppm) 7.11 (dd, 1H, *J* = 15.2, 10.8 Hz), 5.98 (bs, 1H, NH), 5.94 (dd, 1H, *J* = 15.2, 10.8 Hz), 5.80 (d, 1H, *J* = 15.2 Hz), 5.73 (d, 1H, *J* = 15.2 Hz), 1.79 (m, 3H), 1.52 (m, 6H), 1.42 (d, 6H, *J* = 2.4 Hz), 1.26 (s, 9H). <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>–CD<sub>3</sub>CN (1:1)) δ (ppm) 165.6, 152.4, 140.4, 124.7, 123.8, 50.9, 41.8, 36.8, 35.6, 28.6 (2C). HRMS C<sub>19</sub>H<sub>29</sub>NO [M + H<sup>+</sup>]: 288.2327. Found: 288.2315.

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**Supporting Information Available:** Experimental details and copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all the coupling products. Crystallographic data in CIF format for the major coupling product from Table 5, entry 5. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(46) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.