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Investigations on the Suzuki−Miyaura and Negishi Couplings with Alkenyl Phosphates: Application to the Synthesis of 1,1-Disubstituted Alkenes

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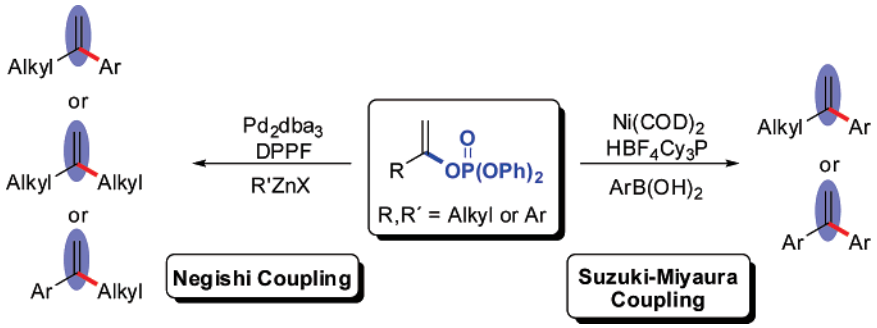

The development of versatile Suzuki−Miyaura and Negishi cross-couplings with nonactivated alkenyl phosphates and aromatic boronic acids or organozinc reagents was achieved in acceptable to good yields. A series of 1,1-disubstituted alkenes were synthesized using a combination of either $Ni(COD)_2/Cy_3P/K_3PO_4$ or Pd_2dba_3/DPPF in THF. When working with alkenyl electrophiles in metal-catalyzed cross-couplings, this method lends itself as a less costly and more stable alternative to the corresponding triflate or nonaflate derivatives. In addition, initial studies are presented regarding an efficient 1,2-migration under Negishi coupling conditions.

Introduction

During the past decade, substantial efforts have been devoted in attempts to expand the scope of substrates capable of forming new C−C bonds in metal-catalyzed cross-couplings and vinyl substitution reactions.[1] Especially aryl chlorides have proven their worth as viable coupling partners in Pd-catalyzed reactions despite their reluctance to undergo oxidative addition.[2,3] Typically, the coupling of less activated electrophiles requires an electron-rich palladium catalyst. This is often obtained by using highly electron-donating ligands such as alkyl phosphines or carbenes.[4] Furthermore, alkenyl phosphates and tosylates have been utilized with great success in various reactions such as the Stille,[5] Negishi,[6] Suzuki−Miyaura,[5a,7] Kumada,[8] Sonogashira,[5a,9] Buchwald−Hartwig,[8c,10] carbonyl enolate couplings[7e] and in the Heck reaction,[11] providing a reliable alternative to the less stable

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and more expensive alkenyl triflate or nonaflates. However, in this case attention has often been devoted to the α,β-unsaturated carbonyl compounds or α-heteroatom substituted alkenyl counterparts where the oxidative addition step occurs more readily using a triaryl phosphine ligated Pd or Ni catalyst. Expansion of this class of substrates to include the nonactivated alkenyl counterparts has received less attention undoubtedly because of the more difficult oxidative addition step and hence higher requirements to the catalytic system.

In a previous report with nonactivated alkenyl phosphates and tosylates, we disclosed an efficient procedure for promoting the Heck coupling with electron-deficient alkenes.[12] Particularly the alkenyl phosphates proved their usefulness, displaying higher stability than their tosylate and triflate/nonaflate counterparts with no sign of decomposition after being stored for months at −18 °C or being heated at 100 °C in DMF for 24 h. In our pursuit to unveil the full potential of these nonactivated alkenyl phosphate as substrates in metal-catalyzed transformations, a direct synthesis of 1,1-diaryl alkenes by a Ni(0)-catalyzed Suzuki−Miyaura coupling was developed (Scheme 1).[7a] The combination of easily accessible aromatic vinyl phosphates and the vast number of commercially available aryl boronic acids provided easy access to unsymmetrical diaryl alkenes with generally good yields.

SCHEME 1. Suzuki−Miyaura Couplings with Alkenyl Phosphates

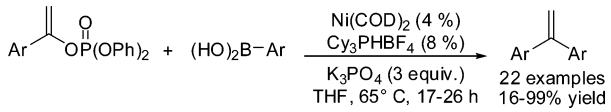
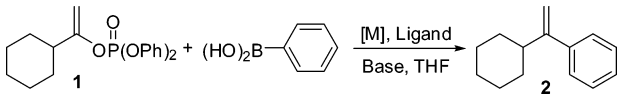


TABLE 1. Optimization of Suzuki Couplings of Alkenyl Phosphates with Phenylboronic Acid



Entry	Metal	Ligand	Base and Additive	Temp °C[a]	Conversion (Yield) of 2[b]
1	$Ni(COD)_2$ (4%)	HBF_4Cy_3P (8%)	K_3PO_4	65	83% (75%)
2	Pd_2dba_3 (2.5%)	X-Phos (10%)	K_3PO_4 + LiCl	70	8%
3	Pd_2dba_3 (2.5%)	$HBF_4(t\text{-Bu})_3P$ (10%)	K_3PO_4 + LiCl	100[c]	-[d]
4	$Ni(COD)_2$ (5%)	HBF_4Cy_3P (10%)	K_3PO_4	75	100% (97%)

[a] Reactions were run in sealed sample vials. [b] Conversions were determined by ^1H NMR spectroscopy. Isolated yield after column chromatography. [c] Reaction run in toluene. [d] No reaction.

Since 1,1-disubstituted alkenes and their saturated counterparts represent an important structural motif in organic synthesis and biologically active compounds, it would be desirable if the above-mentioned method could be expanded to include not only 1,1-diaryl alkenes but also the corresponding 1-aryl-1-alkyl and 1,1-dialkyl alkenes.[13] Different methods are presented in the literature, and Wittig reactions or addition of Grignard reagents to the aryl or alkyl ketone followed by dehydration represent the most general approaches.[14] Some examples exploiting known metal-catalyzed cross-couplings are presented, but they often

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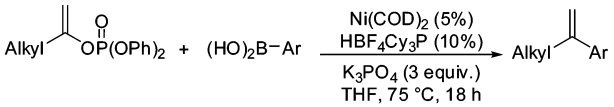
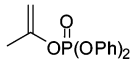
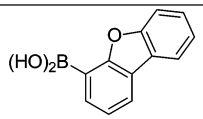
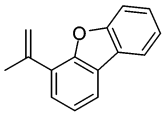
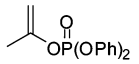
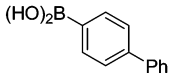
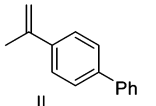
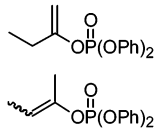
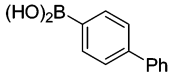
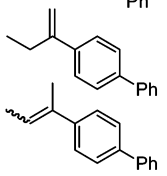
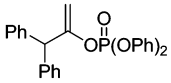
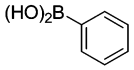
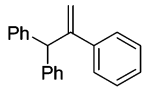
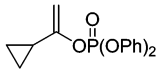
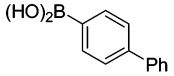
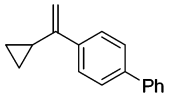
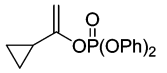
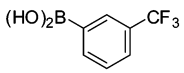
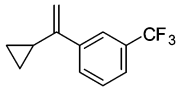
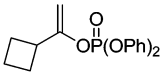
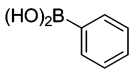
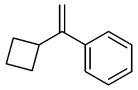
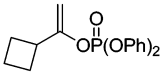
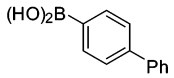
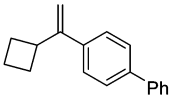
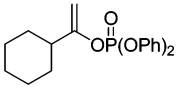
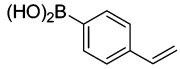
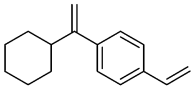
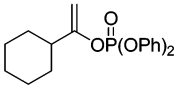
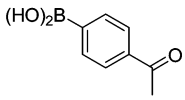
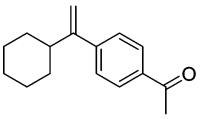
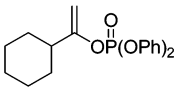
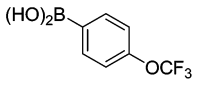
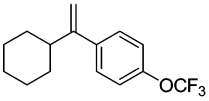
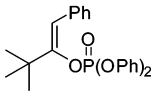
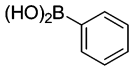
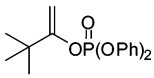
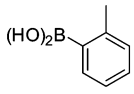
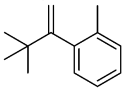
TABLE 2. Suzuki Couplings of Alkyl Vinyl Phosphates with Aryl Boronic Acids[a]



Entry	Alkyl phosphate	Boronic acid	Product	Yield (%)[b]	Compound nr.
1				91[c]	**3**
2				98	**4**
3				78[d]	**5**
4				93	**6**
5				56	**7**
6				56	**8**
7				72	**9**
8				30	**10**
9				69	**11**
10				82	**12**
11				90	**13**
12				57	**14**
13				~10%[e]	**15**
14				~10%[e]	**16**

[a] Reactions were run in sealed sample vials. [b] Isolated yield after column chromatography. [c] Isolated product contains dibenzofurane; see SI. [d] Isolated after hydrogenation. [e] Conversions were determined by ^{1}H NMR spectroscopy. Product not isolated.

rely on the use of the corresponding vinyl halide or less stable vinyl triflate.[15]

Herein, we describe the development of general reaction conditions allowing an easy access to 1,1-disubstituted alkenes in good to excellent yields via Ni(0)- and Pd(0)-catalyzed couplings of nonactivated alkenyl phosphates with aryl boronic acids or organozinc reagents, respectively. In addition, initial studies on the 1,2-migration of the alkenyl palladium intermediate leading to β-alkyl styrenes are presented.

Results and Discussion

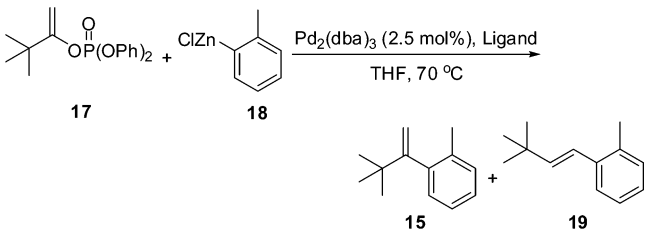
Suzuki−Miyaura Couplings. As mentioned in the Introduction, a catalytic system consisting of $Ni(COD)_2$ (4%) as the nickel source with HBF_4PCy_3 (8%) as the ligand salt combined with K_3PO_4 (3 equiv) as base in THF at 65 °C promoted efficiently the coupling of aromatic alkenyl phosphates with aryl boronic acids.[7a] This system was then initially extrapolated to include alkyl vinyl phosphates. When the *O*-1-cyclohexylvinyl-*O*,*O*-diphenylphosphate **1** was coupled to phenylboronic acid, this resulted in an 83% conversion with a 75% isolated yield of the 1,1-disubstituted alkene (Table 1, entry 1). Longer reaction times unfortunately did not improve the efficiency of this reaction. Changing the solvent to toluene or 2-methyltetrahydrofuran combined with a raise in the reaction temperature only lowered the conversion.

Attempts to change the base confirmed that K_3PO_4 was the proper choice.[16] Changing the catalyst to palladium in combination with the ligands X-Phos and $(t\text{-Bu})_3P$ with added LiCl, systems which previously promoted the oxidative addition step in Heck couplings, resulted in low conversion or no reaction (Table 1, entries 2 and 3).[17] Returning to the original coupling conditions with an increase in catalyst loading to 5% and a raise of reaction temperature to 75 °C in THF gratifyingly led to full conversion and an isolated yield of 97% (Table 1, entry 4).

With these slightly modified reaction conditions at hand, we next tested the generality of the coupling as illustrated in Table 2. Several cyclic and acyclic alkyl vinyl phosphates were coupled in moderate to good yields with different boronic acids carrying both electron-withdrawing (Table 2, entries 6, 10, and 11) and one electron-donating substituent (Table 2, entry 1). The cyclopropyl- and cyclobutyl vinyl phosphates yielded the desired coupling products though in lower yields than the corresponding cyclohexyl vinyl phosphate (Table 2, entries 5−8). This may be due to the chemical instability of the coupling product since full conversion was not obtained with the starting alkyl vinyl phosphate, which was still left in the crude reaction mixture after 18 h.

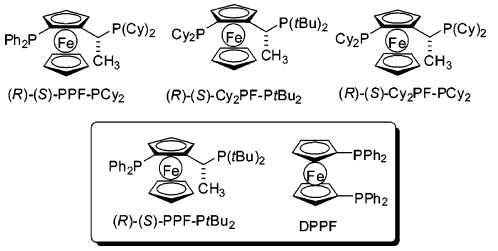
Couplings with 1-cyclohexyl vinyl phosphate usually went to completion, and the desired coupling products could be isolated in good to high yields (Table 2, entries 9−11). These products represent precursors to partially saturated benzophenone derivatives.[18] Cross-couplings with 1-methyl vinyl phosphate generated the propenylated aromatic compounds in high yields (91 and 98%, Table 2, entries 1 and 2). In entry 3, an inseparable mixture of 1-butenyl and 2-butenyl phosphate was examined with 4-biphenylboronic acid providing the coupling product in 78% yield after hydrogenation of the crude reaction mixture. When the coupling of the *Z*-vinyl phosphate shown in entry 12 carrying a phenyl group in the 2-position was attempted, a product resulting from an apparent isomerization was observed. The mechanism for this isomerization is not clear at this point.[19] Further increase of the steric bulk on the C1-position of the alkyl substituents of the vinyl phosphate or in ortho-position on the aryl boronic acid unfortunately leads to lower conversion rates (Table 2, entries 13 and 14). In combination with the sometimes difficult preparation of pure 1-alkyl vinyl phosphates by α-hydrogen abstraction from an unsymmetrical ketone with closely related α-substituents by a kinetic base[12] (Table 2, entry 3) led us to search for an alternative catalytic system to overcome these restrictions.

TABLE 3. Optimization of Negishi Cross-Coupling with Alkenyl Phosphates[a]



Entry	Ligand	Conversion (%)[b] (Yield %)	Ratio 15/19
1	DPPF	100 (74)	99/1
2	(*R*)-(*S*)-PPF-PCy_2	0	
3	(*R*)-(*S*)-Cy_2PF-PCy_2	0	
4	(*R*)-(*S*)-Cy_2PF-P*t*Bu_2	100[c]	43/57
5	P(*t*Bu)$_3$	n.d.[d]	72/28
6	(*R*)-(*S*)-PPF-P*t*Bu_2	100[c]	1/99

[a] Reactions were run in sealed sample vials. [b] Conversions measured by ^{1}H NMR spectroscopy. [c] Formation of a byproduct (see Discussion for Scheme 4). [d] Not determined.



(15) For some examples, see: (a) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. (b) Ganchegui, P.; Bertus, P.; Szymoniak, J. *Synlett* **2001**, 123. (c) Blatter, K.; Schlüter, A.-D. *Synthesis* **1989**, *5*, 356. (d) Blough, B. E.; Abraham, P.; Lewin, A. H.; Kuhar, M. J.; Boja, J. W.; Carroll, F. I. *J. Med. Chem.* **1996**, *39*, 4027. (e) Strachan, J.-P.; Sharp, J. T.; Parsons, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 807. (f) Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2003**, *6*, 1091. (g) Kundo, K.; McCullagh, J. V.; Morehead, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (h) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719. (i) Amatore, M.; Gosmini, C.; Périchin, J. *Eur. J. Org. Chem.* **2005**, 989.

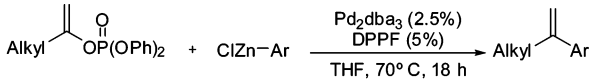
(16) For the use of K_3PO_4 as base in Suzuki−Miyaura couplings, see: Chen, C.; Yang, L.-M. *Tetrahedron Lett.* **2007**, *48*, 2427 and references therein.

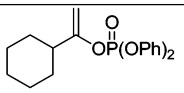
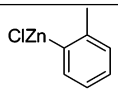
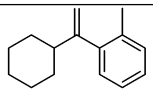
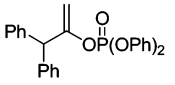
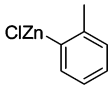
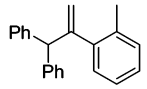
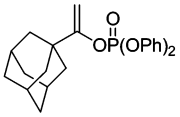
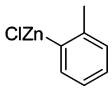
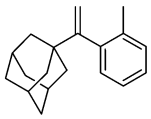
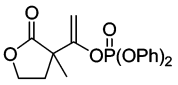
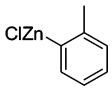
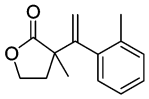
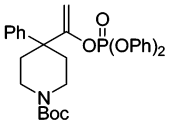
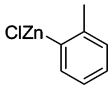
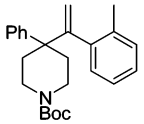
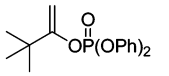
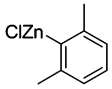
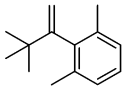
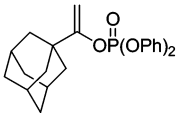
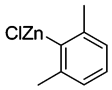
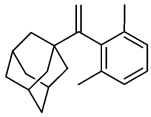
(17) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931.

(18) Used in the synthesis of (*S*)-oxybutynin. See: Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231.

(19) One reviewer pointed out the possibility of a mechanism involving a Ni-catalyzed hydroarylation of the corresponding alkyne with the aryl boronic acid (Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2001**, 2688). Although plausible, this mechanism would require that the vinyl phosphate undergo elimination with formation of the alkyne. Heating the same vinyl phosphate with potassium phosphate in THF at 75 °C for 24 h did not lead to the formation of 3,3-dimethyl-1-phenylbutyne. In addition, formation of the requisite aryl nickel hydride species for the hydroarylation step requires the presence of water in the reaction media. Further investigations on the mechanism behind this isomerization are being conducted and will be reported in due time.

TABLE 4. Negishi Cross-Couplings with Alkyl Vinyl Phosphates and Aryl Zinc Reagents[a]

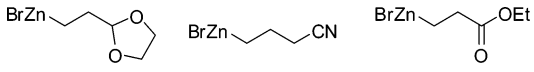


Entry	Alkyl phosphate	Aryl Zinc Chloride	Product	Yield (%)[b]	Compound nr.
1				92	**20**
2				86	**21**
3				80	**22**
4				70[c]	**23**
5				55[d]	**24**
6				67	**25**
7				52[e]	**26**

[a] Reactions were run in sealed sample vials. [b] Isolated yield after column chromatography. [c] 78% conversion measured by ^{1}H NMR spectroscopy. [d] 63% conversion measured by ^{1}H NMR spectroscopy. [e] 65% conversion measured by ^{1}H NMR spectroscopy.

Negishi Couplings. Attention was then turned toward the palladium-catalyzed Negishi couplings because these reactions, like the Suzuki−Miyaura couplings, are characterized by their good functional group tolerance and high reactivity of the organozinc reagents.[1b,4a,6,20] We set out to identify reaction conditions capable of promoting the coupling between *t*-butyl vinyl phosphate **17** and the organozinc reagent **18**[4a] (Table 3), a coupling that provided less than 10% conversion using our Suzuki coupling conditions mentioned above. After a brief screening, it was quickly discovered that DPPF as the ligand in combination with Pd_2dba_3 in THF at 70 °C afforded the desired coupling with full conversion and an isolated yield of 74% (Table 3, entry 1). Screening of other ferrocenyl-based ligands of the Josiphos type did not improve the reaction at first (Table 3, entries 2 and 3). On the other hand, when the (*R*)-(*S*)-Cy_2-PF-P*t*Bu_2 ligand was applied full conversion was once again observed, but more interestingly a mixture of products **15** and **19** was obtained where **19** is the result of a 1,2-palladium migration (Table 3, entry 4).[12,17] Surprisingly, performing the coupling with (*t*-Bu)$_3$P, a ligand which previously promoted the rearrangement of the same vinyl phosphate in Heck reactions, led to the preferential formation of the nonmigrated product (Table 3, entry 5). Complete conversion and rearrangement to the coupling product **19** could nevertheless be obtained by applying the (*R*)-(*S*)-PPF-P*t*Bu_2 ligand (Table 3, entry 6).

SCHEME 2. Commercially Available Organozinc Bromide Reagents



27 **28** **29**

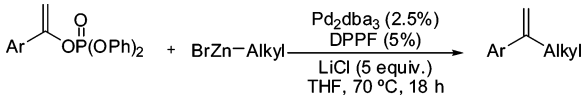
Changing the counterion on the organozinc reagent from chloride to bromide stopped the reaction, proving the importance of the presence of chloride ions in the reaction mixture.[21] The chloride ion is speculated to form a reactive palladium(0)−chloride anionic complex, facilitating the oxidative addition step.[22]

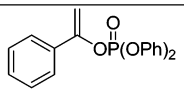
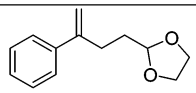
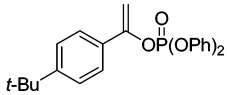
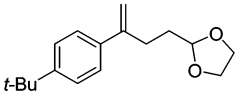
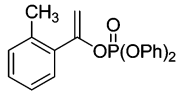
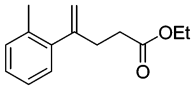
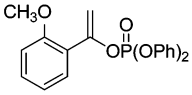
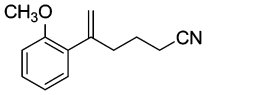
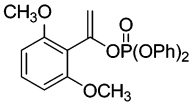
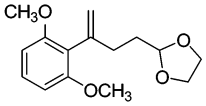
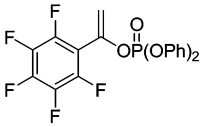
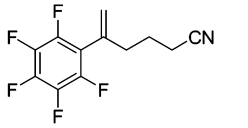
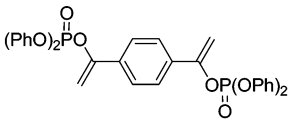
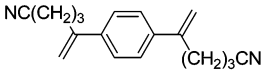
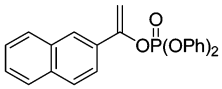
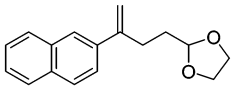
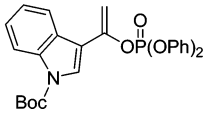
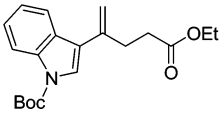
As seen in Table 4, these conditions proved to be tolerable to steric factors, allowing the coupling to proceed with several bulky vinyl phosphates in acceptable yields. Entries 3−5 illustrate examples of vinyl phosphates carrying C1-quaternary

(20) For reviews and general literature on the Negishi reaction, see: (a) *Organozinc Reagents: A Practical Approach;* Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (b) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (d) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838. (e) Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2916. (f) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762. (g) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brian, C. J.; Valente, C. *Chem.−Eur. J.* **2006**, *12*, 4749. (h) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (i) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (j) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594. (k) Hadei, N.; Kantchev, E. A. B.; O'Brian, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3085. (l) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. (m) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82. (n) Hou, S. *Org. Lett.* **2003**, *5*, 423. (o) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (p) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(21) During the formation of the organozinc reagent, ≥1 equiv of LiCl is formed. See ref 4a.

TABLE 5. Negishi Cross-Couplings with Aryl Vinyl Phosphates and Alkylzinc Reagents[a]



Entry	Aryl Phosphate	Alkyl Zinc Bromide	Product	Yield (%)[b]	Compound nr.
1		**27**		75	**30**
2		**27**		70	**31**
3		**29**		51	**32**
4		**28**		80	**33**
5		**27**		95	**34**
6		**28**		60	**35**
7		**28**		42	**36**
8		**27**		83	**37**
9		**29**		55	**38**

[a] Reactions were run in sealed sample vials. [b] Isolated yield after column chromatography.

carbons all yielding the desired product in acceptable to good yields. Changing to the (2,6-dimethylphenyl)zinc(II) chloride slightly lowered the conversion rates and yields (Table 4, entries 6 and 7).

Aryl vinyl phosphates, which were previously used to generate the 1,1-diaryl alkenes,[7a] were then evaluated in couplings with alkyl organozinc reagents. For this purpose, the commercially available organozinc bromides in Scheme 2 were examined. As noticed earlier during the optimization study mentioned above, the organozinc bromides were not reactive, but the addition of 5 equiv of LiCl to the reaction mixture afforded the desired coupling.

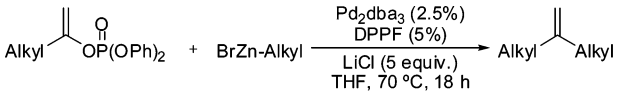
Several aryl vinyl phosphates with different substitution patterns were tested, and all coupled with satisfactory yields (Table 5). Even increasing the steric bulk in the ortho-position of the aryl moiety did not affect the coupling yield (Table 5, entries 3−5). Aryl vinyl phosphates carrying electron-donating and -withdrawing groups were reactive, although the pentafluorophenyl vinyl phosphate was less reactive (Table 5, entries 4−6). A double cross-coupling was also attempted with the divinyl diphosphate in entry 7, furnishing 42% of the divinyl-substituted benzene. Finally, a vinyl phosphate carrying an indole moiety proved also sufficiently reactive under these conditions (Table 5, entry 9).

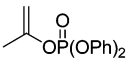
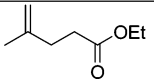
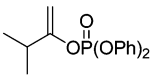
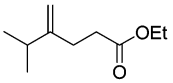
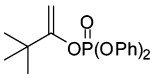
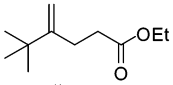
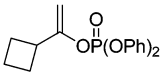
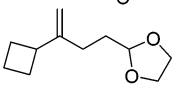
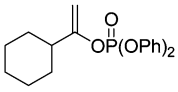
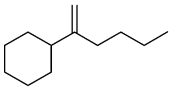
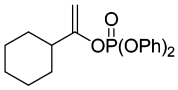
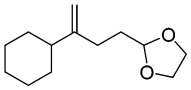
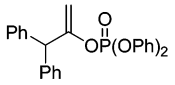
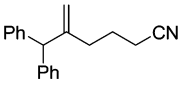
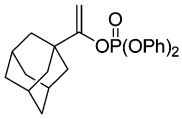
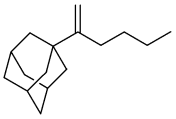
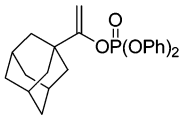
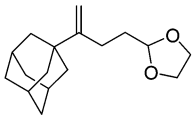
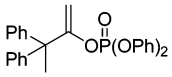
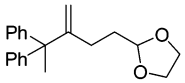
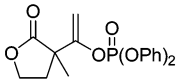
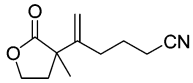
Attention was then turned toward the 1,1′-dialkyl-substituted alkenes to test if this final class of compounds could be synthesized in a similar manner. Again, we chose to utilize the alkylzinc bromide reagents in combination with added LiCl since they are commercially available and hence provide easy access to the desired compounds. To our satisfaction, the same catalytic system proved sufficiently reactive without further optimization (Table 6).

As with the other above-mentioned Negishi couplings, the substitution pattern on the C1-carbon of the vinyl phosphates

(22) The presence of excess LiCl may augment the concentration of a more reactive anionic Pd(0) complex in equilibrium with its neutral species. See: (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *21*, 2271. (b) Högermeier, J.; Reissig, H.-U.; Brüdgam, I.; Hartl, H. *Adv. Synth. Catal.* **2004**, *346*, 1868. (c) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.* **2006**, *47*, 1325. (d) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079. (e) Camp, D.; Matthews, C. F.; Neville, S. T.; Rounes, M.; Scott, R. W.; Truong, Y. *Org. Process Res. Dev.* **2006**, *10*, 814. (f) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (g) Cameron, M.; Foster, B. S.; Lynch, J. E.; Shi, Y.-J.; Dolling, U.-H. *Org. Process Res. Dev.* **2006**, *10*, 398.

TABLE 6. Negishi Cross-Couplings with Alkyl Vinyl Phosphates and Alkylzinc Reagents[a]



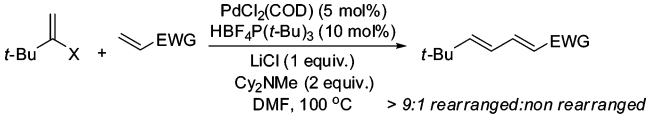
Entry	Alkyl Phosphate	Alkyl Zinc Bromide	Product	Yield (%)[b]	Compound nr.
1		**29**		25[c]	**39**
2		**29**		57	**40**
3		**29**		20[d]	**41**
4		**27**		51	**42**
5		*n*-BuZnBr		50	**43**
6		**27**		92	**44**
7		**28**		77	**45**
8		*n*-BuZnBr		94	**46**
9		**27**		72	**47**
10		**27**		86	**48**
11		**28**		81	**49**

[a] Reactions were run in sealed sample vials. [b] Isolated yield after column chromatography. [c] Product is volatile. [d] 50% conversion based on the ^{1}H NMR spectrum of the crude reaction mixture.

did not affect the reaction, which in most cases went to full conversion. Unexpectedly, the *t*-butyl vinyl phosphate proved to be less reactive (50% conversion, Table 6, entry 3) when coupled with an organozinc reagent carrying an alkyl chain compared to its aryl counterpart where full conversion was obtained (Table 3, entry 1). Even a more strained system such as the cyclobutyl vinyl phosphate turned out to be sufficiently reactive with an alkyl zinc reagent leading to a 51% coupling yield (Table 6, entry 4). Moreover, when couplings with the methyl vinyl phosphate and isopropyl vinyl phosphates were conducted, low yields were obtained after column chromatography, probably due to the low boiling point of the isolated compounds (Table 6, entries 1 and 2).

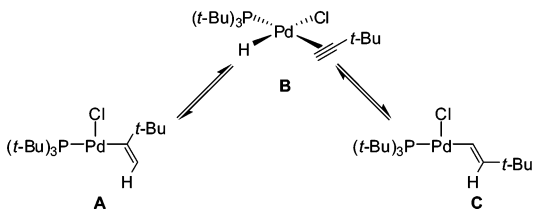
Negishi Couplings of Alkenyl Phosphates with 1,2-Migration. During the ligand optimization studies for the Negishi coupling between alkyl vinyl phosphates and *o*-tolyl zinc chloride, a coupling product was detected resulting from a 1,2-migration (Table 3, entries 4−6). We have previously reported on effective Pd-catalyzed 1,2-migrations in Heck couplings with

SCHEME 3. Proposed Mechanism for the 1,2-Migration in the Heck Reaction

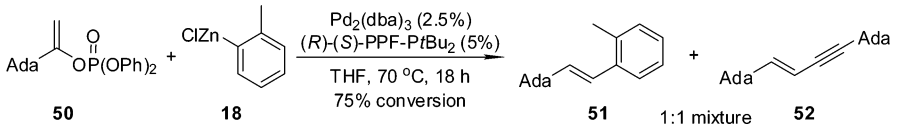


X=OTs, 72-95%
X=OP(O)(OPh)$_2$, 64-77%

Proposed Mechanism



SCHEME 4. Negishi Cross-Coupling under Conditions Favoring 1,2-Migration with Formation of a Byproduct



alkenyl tosylates and phosphates possessing a quaternary C1-carbon using $(t\text{-Bu})_3$P as the ligand in combination with LiCl in DMF (Scheme 3).[12,17]

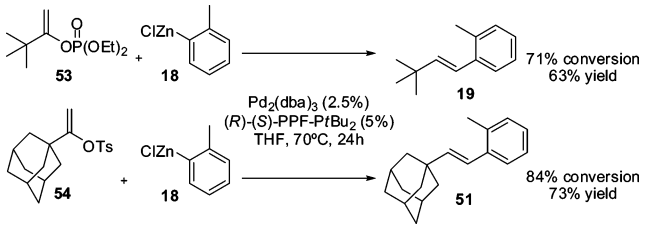
The proposed mechanism for this 1,2-migration in the Heck reactions starts with the complex **A** formed after the oxidative addition step.[23] Since the complex **A** is tricoordinated, it deviates from the normally known tetracoordinated square-planar complexes by possessing a free coordination site on the palladium nucleus. This free coordination site then facilitates *cis*-β-hydride elimination, generating the *t*-butylacetylene palladium(II) hydride complex **B**. Rotation of the acetylene and hydropalladation affords the rearranged complex **C**. DFT calculations carried out on this system suggested this rearrangement to be in a fast equilibrium and that discrimination of the two intermediates is dictated by the different rates of the carbopalladation step.[12]

The above proposed mechanism can be easily applied to explain the results for the Negishi couplings using the $(t\text{-Bu})_3$P ligand as seen in Table 3, entry 5, although in this case higher selectivity for the nonmigrated product was obtained. On the other hand, the rearrangement noted with the bidentate Josiphos ligands is more surprising since the bidentate coordination of the ligand would occupy the free site on the palladium nucleus, hence blocking the β-hydride elimination (Table 3, entries 4 and 6).[8b] One explanation for these observations could be that the diphenylphosphine moiety on the ferrocene unit briefly dissociates from the palladium center, leaving a complex similar to **A** (Scheme 3), allowing rearrangement to take place before recoordination of the ligand and transmetalation with the organozinc reagent.

During the coupling of the *t*-butyl vinyl phosphate **17** to **18**, a byproduct was formed using the conditions favoring 1,2-migration. The same reaction was conducted with the similar adamantyl vinyl phosphate, and analyzing the crude reaction mixture by proton NMR revealed a 1:1 mixture of the 1,2-migrated product and the byproduct, which upon purification was identified as the (*E*)-1,4-diadamantyl-buten-3-yne (**52**) (Scheme 4).[24] Since full conversion was not obtained, it was speculated that formation of **52** occurs via base-induced reductive elimination/deprotonation of the palladium hydride complex **B** (Scheme 3) releasing adamantyl acetylene into solution. This alkyne is then deprotonated by another equivalent of *o*-tolyl zinc chloride, forming a reactive (adamantylethynyl)zinc(II) chloride which competes in the transmetalation step with *o*-tolyl zinc chloride with another round of complex **C** forming **52**.[25]

Two other alkenyl derivatives were then tested in the coupling to examine the influence of the leaving group (Scheme 5).

SCHEME 5. Negishi Cross-Couplings with 1,2-Migration



Gratifyingly, both the *t*-Bu vinyl *O*,*O*-diethyl phosphate **53** and the adamantyl vinyl tosylate **54** proved reactive utilizing the catalytic system at hand. But more interestingly, both provided only the desired 1,2-migrated product **19** and **51**, respectively, without formation of byproducts or decomposition of the starting materials. Since a simple change in the electrophile eliminates the formation of **52**, the generation of the intermediate adamantyl acetylene must occur by a mechanism different from that suggested above. Slow base elimination of one of the olefin protons on the vinyl phosphate **50** to generate an alkyne could potentially explain this observation. Additional work is currently in progress to identify the optimal conditions for this interesting rearrangement and hopefully to gain further mechanistic insight.

Conclusion

We have successfully developed standard reaction conditions for the Suzuki−Miyaura and Negishi couplings of nonactivated alkenyl phosphates with boronic acids and organozinc reagents, providing a direct and facile access to a diverse array of 1,1-disubstituted alkenes. This work, in combination with our previous report, allows for the formation of almost any carbon−carbon bond adjacent to the alkenyl moiety, making these methods versatile tools for the synthetic organic chemist. In addition, initial studies regarding an efficient 1,2-migration of the alkenyl palladium(II) intermediate were presented, providing a new variation of the Negishi cross-coupling.

Experimental Section

2-(4-Biphenyl)propene (4). General Procedure for the Suzuki−Miyaura Couplings of Nonactivated Vinyl Phosphates with Boronic Acids. Propen-2-yl diphenylphosphate (87.1 mg, 0.30 mmol), 4-biphenylboronic acid (89.1 mg, 0.45 mmol), K_3PO_4 (191 mg, 0.90 mmol), and HBF_4PCy_3 (11.0 mg, 0.030 mmol) were dissolved in THF (3 mL). $Ni(COD)_2$ (4.1 mg, 0.015 mmol) was then added, and the sample vial was fitted with a Teflon sealed screw cap and removed from the glovebox. The reaction mixture was heated for 18 h at 75 °C, after which it was filtered through a plug of Celite and washed with diethyl ether. After concentration in vacuo, the crude product was purified by flash chromatography on silica gel using pentane as eluent. This afforded 58.0 mg of the title compound (98% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67−7.59 (m, 6H), 7.49 (m, 2H), 7.39 (m, 2H), 5.49 (d, 1H, J = 0.4 Hz), 5.17 (m, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.9, 140.9, 140.3, 140.2, 128.9, 127.4, 127.1, 127.0, 126.0, 112.6, 21.9. GC−MS $C_{15}H_{14}$ [M]: calcd, 194; found, 194.

(23) (a) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184. (b) Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007**, *26*, 550. (c) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758.

(24) Palladium-catalyzed dimerizations of alkynes are known but since the presence of *o*-tolyl zinc chloride would result in deprotonation of the alkyne formed in situ, it is believed that **52** is formed by a different mechanism. See: (a) Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002**, *67*, 591. (b) Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 11107.

(25) The fact that (adamantylethynyl)zinc(II) chloride transmetalates faster than *o*-tolyl zinc chloride was confirmed by increasing the steric bulk on the organozinc reagent to the *m*-xylene derivative, resulting in sole formation of the byproduct **52**.

2-[3-(2,6-Dimethoxyphenyl)but-3-enyl]-1,3-dioxolane (34). General Procedure for the Negishi Couplings of Nonactivated Vinyl Phosphates with Organozinc Reagents. 1-(2,6-Dimethoxyphenyl)-vinyl diphenylphosphate (164.9 mg, 0.40 mmol), DPPF (11.1 mg, 0.02 mmol), and lithium chloride (84.8 mg, 2.00 mmol) were dissolved in THF (2.0 mL) in a 7-mL sample vial in a glovebox, where after a 0.5 M solution of [2-(1,3-dioxolanyl)ethyl] zinc bromide in THF (1.0 mL, 0.48 mmol) was then added. Pd_2dba_3 (9.16 mg, 0.01 mmol) was added, and the sample vial was fitted with a Teflon sealed screw cap and then removed from the glovebox. The reaction mixture was heated for 18 h at 70 °C, after which it was concentrated in vacuo, and then the crude product was purified by flash chromatography on silica gel using dichloromethane as the eluent. This afforded 100 mg of the title compound (95% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 7.22 (t, 1H, J = 8.4 Hz), 6.65 (d, 2H, J = 8.4 Hz), 5.26 (d, 1H, J = 0.8 Hz), 4.83 (t, 1H, J = 4.8 Hz), 4.79 (m, 1H), 3.86 (m, 2H), 3.78 (m, 2H), 3.75 (s, 6H), 2.40 (t, 2H, J = 7.6 Hz), 1.64 (m, 2H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm) 158.5, 143.5, 129.3, 121.0, 115.4, 105.1, 104.8, 65.5, 56.4, 33.1, 32.3. HRMS $C_{15}H_{20}O_2$ [M + Na^+], 287.1259; found, 287.1275.

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, the Danish Natural Science Research Council, the Carlsberg Foundation, and the University of Aarhus. We thank Solvias for a generous gift of the Josiphos ligands.

Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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