JOC Article

Regioselective Heck Vinylation of Electron-Rich Olefins with Vinyl Halides: Is the Neutral Pathway in Operation?

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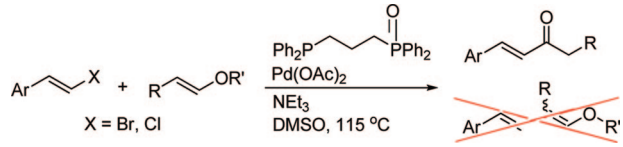

Highly regioselective vinylation of electron-rich olefins by bromo- as well as chlorostyrenes is effected by palladium catalysis with either mono- or bidentate phosphines in a molecular solvent, with no need for halide scavengers, ionic liquids, or ionic additives. The use of the hemilabile 1,3-bis(diphenylphosphino)propane monoxide (dpppO) as a ligand led to faster reactions of more challenging 2-substituted vinyl ethers and reduced Pd loadings. In contrast to the related arylation reaction, evidence suggests that the vinylation may proceed via the neutral Heck mechanism.

Introduction

The Heck reaction has become an indispensable tool for the formation of C−C bonds, finding its place in many different areas of synthetic organic chemistry.[1] For the reaction concerning electron-deficient olefins (R′ = EWG, Scheme 1), the products usually result from aryl/vinylation at the terminal β position.[2] However, under similar conditions with electron-rich olefins (R′ = EDG, Scheme 1), regioselectivity can be poor, and in fact, a mixture of products is often obtained.[2e,g−i,3−5] This is exemplified by the arylation of butyl vinyl ether with p-RC_6H_4Br (R = OMe, NMe_2) catalyzed by Herrmann−Beller's palladacycle[6] and Fu's Pd−P(t-Bu)$_3$ system,[7] which gave poor α/β selectivities of 10/13 and 4/1, respectively. It is widely

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believed that this problem arises from competing reaction pathways, which result in different regioisomers (Scheme 1).[3−5,7,8]

Several methods have been successfully employed to overcome this problem, bringing the selectivity up to a synthetically useful level. This success is usually attributed to promoting the "ionic" pathway **A**, which leads to internal α substitution.[10−12] Taking the lead from Hallberg's pioneering work,[13] triflates, tosylates, and mesylates have been utilized as labile counterions in Heck reactions of electron-rich olefins. Unfortunately, problems such as poor availability, high cost, and thermal lability limit their synthetic utility.[5,8,14] It was shown by Cabri that bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp) could effect the aryl/vinylation of electron-rich olefins with almost exclusive α substitution.[5] Ligands of this type are now used as the standard for internal arylation reactions. In addition to this, halide scavengers such as silver or thallium salts drastically improve the regioselectivity for reactions of aryl/vinyl bromides.[8g,j] However, the cost of silver and toxicity of thallium prevent their use on larger scales, particularly as more than stoichiometric quantities are often needed.

Recent work in this group has revealed that the use of imidazolium-based ionic liquids in conjunction with Pd−dppp catalysis offers excellent levels of regioselectivity with aryl bromides.[15] It is assumed that the ionic environment provided by the solvent makes generation of the cationic species more facile (Scheme 1), and this is echoed by the recent kinetic studies of Amatore, Jutand, and co-workers.[12] In addition, it was found that hydrogen-bond-donating salts such as $[HNEt_3][BF_4]$ could increase both the rate and selectivity in ionic as well as molecular solvents, presumably by facilitating dissociation of bromide from Pd(II).[15d] Further development led to the discovery that alcohol solvents such as ethylene glycol and *i*-PrOH, with their large hydrogen-bond-donating ability, allow expedient and highly selective arylation of electron-rich olefins.[16,17] Larhed recently showed that water can also be an excellent solvent for the arylation reaction in terms of rate and selectivity, although this method seems to be limited to 2-hydroxy vinyl ether as the olefin.[18]

SCHEME 1. Heck Reaction and the Key Ionic and Neutral Species, Where R = Aryl/Vinyl, R′ = EDG/EWG, and X = Halide/Triflate

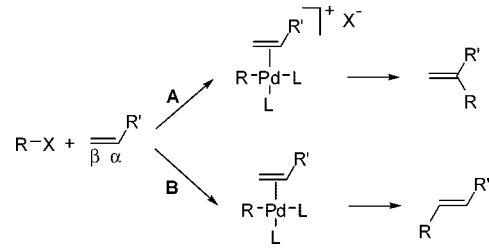
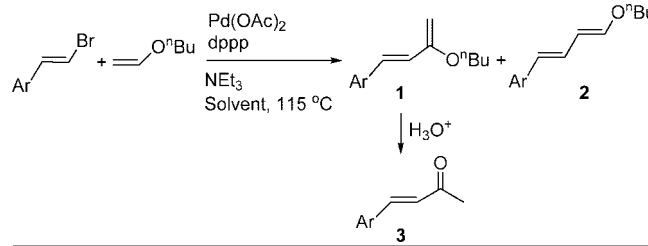


TABLE 1. Vinylation of BVE in Ionic Liquid vs DMSO[a]



entry	solvent	additive[b]	time (h)	conv (%)	selectivity[c]
1	[bmim][BF_4]	none	20	40	>99:1
2	[bmim][BF_4]	[$HNEt_3$][BF_4]	20	33	>99:1
3	DMSO	none	0.5	61	>99:1
4	DMSO	[$HNEt_3$][BF_4]	0.5	66	>99:1

[a] Reaction conditions: *p*-methoxy-β-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol %), dppp (6 mol %), and NEt_3 (3 mmol) in 2 mL of solvent at 115 °C; conversion measured by ^{1}H NMR. [b] 1.5 mmol added where appropriate. [c] Molar ratio of **1/2** >99:1 assigned when **2** was not detected by ^{1}H NMR and GC.

While generally treated as analogous to arylation, the vinylation of electron-rich olefins is relatively unexplored. Early work by Hallberg et al. showed that although high selectivity for branched products could be achieved in the reaction of vinyl iodides and triflates with 3 mol % of $Pd(PPh_3)_4$ in DMSO, the selectivity was highly substrate-dependent.[13a] Thus, complete reversal of the selectivity was observed when switching from an electron-rich triflate to an electron-deficient bromide. The realization by Cabri that bisphosphine ligands increase the α-selectivity of arylation reactions was taken on board by those studying the vinylations. These ligands have been routinely used since then to obtain the required regioisomer.[8a,g,14a] For instance, using Pd−dppp as catalyst, Skrydstrup et al. addressed some of the problems associated with the use of vinyl triflates by using the less expensive mesylates and tosylates as vinylating agents.[14a] Excellent regioselectivity and good to excellent yields were obtained for the coupling of enamides and electron-deficient mesylates and tosylates. However, with vinyl bromides, halide scavengers such as TlOAc appear still necessary to achieve high regioselectivity.[8g] Thus, there is a need to improve the protocols most commonly employed for the vinylation of electron-rich olefins.

Results and Discussion

As a starting point for our study on the vinylation of electron-rich olefins, we applied the arylation conditions developed within this group to the reaction of *p*-methoxy-β-bromostyrene with *n*-butyl vinyl ether (BVE).[15] Table 1 shows the results obtained with 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]-

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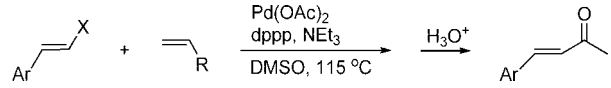
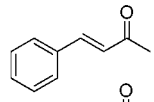
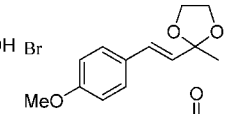
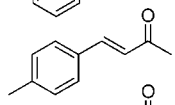
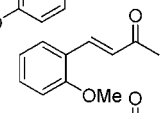
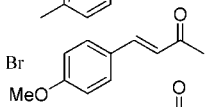
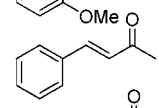
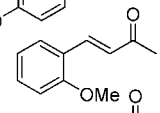
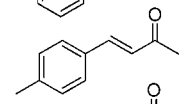
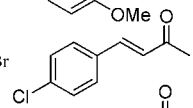
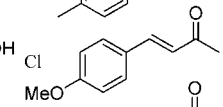
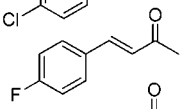
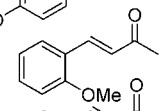
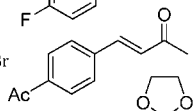
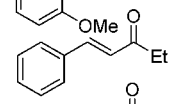
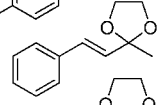
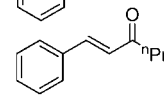
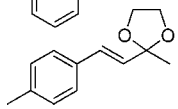
TABLE 2. Regioselective Heck Vinylation of Electron-Rich Olefins with Pd−dppp in DMSO[a]



Entry	Olefin	X	Product	t (h)	Yield (%)	Entry	Olefin	X	Product	t (h)	Yield (%)
1	O^nBu	Br		4	96	10[b]	$O(CH_2)_2OH$	Br		3	82
2	O^nBu	Br		4	91	11	$O(CH_2)_2OH$	Br		3	82
3	O^nBu	Br		3	82	12[c]	$O(CH_2)_2OH$	Cl		27	70
4	O^nBu	Br		3	80	13[c]	$O(CH_2)_2OH$	Cl		27	66
5	O^nBu	Br		4	75	14[c]	$O(CH_2)_2OH$	Cl		24	76
6	O^nBu	Br		4	70	15[c]	$O(CH_2)_2OH$	Cl		24	64
7	O^nBu	Br		5	65	16[c]	OEt	Br		16	80
8[b]	$O(CH_2)_2OH$	Br		4	97	17[c]	OEt	Br		20	65[d]
9[b]	$O(CH_2)_2OH$	Br		4	86						

[a] Reaction conditions: vinyl halide (1 mmol), vinyl ether (3 mmol), $Pd(OAc)_2$ (3 mol %), dppp (6 mol %), NEt_3 (3 mmol) in 2 mL of DMSO at 115 °C. Following the coupling reaction, HCl was added at rt. Isolated yields given. No β-vinylation product was detected by ^1H NMR. [b] As in footnote a but without hydrolysis. [c] Conditions as in footnote a, but $Pd(OAc)_2$ (5 mol %) and dppp (10 mol %) were used. [d] Conversion measured by ^1H NMR.

$[BF_4]$) as solvent. In contrast to the analogous *arylation*,[15] the Pd-dppp-catalyzed *vinylation* was sluggish in the ionic liquid, and addition of hydrogen-bond-donating salts did not have an accelerating effect on the rate (entries 1 and 2).

However, the reaction proceeded very well in DMSO, affording over 60% conversion in just 0.5 h (entry 3). And significantly, the reaction exhibited remarkable selectivity for the products resulting from α substitution, as no linear product could be detected by ^1H NMR or GC. Again, the addition of hydrogen-bond-donating salts had only a negligible effect on the rate (entry 4). A limited screening of conditions revealed that DMSO as solvent and NEt_3 as base gave the best results.

These results show that the α-vinylation of electron-rich olefins catalyzed by Pd-dppp can work in a common, molecular solvent with no need for any additives. By applying the protocol used for Table 1, it was found that the reaction of β-bromostyrene was finished in 4 h. The only side product of the reaction was trace amounts of the dimer resulting from homocoupling of the starting bromide. As can be seen in Table 2 (entry 1), hydrolysis of **1** and subsequent purification led to the desired ketone **3** in an excellent 96% yield.

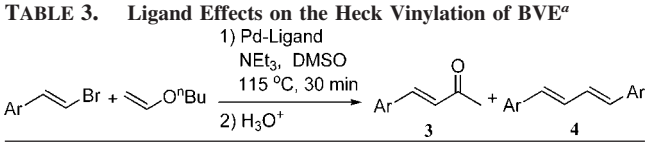
With the conditions for the vinylation in hand, we next investigated the scope of the reaction with respect to vinyl halides and electron-rich olefins. The results are summarized in Table 2. In general, reactions featuring electron-rich bromides such as *p*-methoxy-β-bromostyrene were complete in slightly shorter times. Worthy of particular mention is the reaction of *p*-acetyl-β-bromostyrene (entry 7), the product of which would be difficult to achieve via a conventional aldol methodology. In addition to BVE, 2-hydroxyethyl vinyl ether allowed access to cyclic ketals under identical conditions (entries 8−10). The formation of a protected ketone in this way could be potentially useful when chemoselectivity would otherwise be troublesome. Unfortunately, ketals bearing methoxy groups on the aromatic ring were somewhat unstable in solution, and traces of the corresponding ketone were detectable by ^1H NMR after several hours. For convenience, the 2-methoxy compound was therefore hydrolyzed and isolated as the ketone (entry 11).

Remarkably, vinyl chlorides also reacted, affording exclusively branched products, *albeit* over longer reaction times. Again, these products were hydrolyzed and isolated as the ketones in good yields (entries 12−15). Very few examples of Heck reactions of vinyl chlorides exist in the literature.[19] To our knowledge, these are the first examples with an electron-rich olefin.

Another reaction that was interesting to us was that of 2-substituted vinyl ether with a vinyl halide, as this would lead to products other than methyl ketones. However, reactions with

(19) Examples of Heck coupling with vinyl chlorides: (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6995. (b) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *Synlett* **1994**, 189. (c) Horino, H.; Inoue, N.; Asao, T. *Tetrahedron Lett.* **1981**, *22*, 741.

TABLE 3. Ligand Effects on the Heck Vinylation of BVE[a]



entry	ligand	conv (%)	selectivity **3**:**4**
1	PPh_3	80	80:20
2	$P(4\text{-}OMePh)_3$	86	90:10
3	$P(2\text{-}OMePh)_3$	86	90:10
4	$P[3,5\text{-}(CF_3)_2Ph]_3$	94	>99:1
5	PCy_3	55	>99:1
6	dppm	37	>99:1
7	dppe	36	>99:1
8	dppp	61	>99:1
9	dppb	90	95:5
10	$(2\text{-}CF_3Ph)_2P(CH_2)_3P(2\text{-}CF_3Ph)_2$	86	>99:1
11	dpppO	95	>99:1

[a] Reaction conditions: *p*-methoxy-β-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol %), ligand (6 mol % of bisphosphine or 9 mol % of monophosphine), NEt_3 (3 mmol) in 2 mL of solvent at 115 °C for 30 min; no **2** was detected.

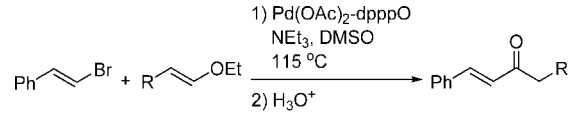
these olefins, which are known to be less reactive,[20] were much slower than with BVE. Thus, even with the catalyst loading increased to 5 mol %, 1-propenyl ether took 16 h to complete (entry 16); with 1-butenyl ethyl ether, complete conversion could not be reached, even with long reaction times (entry 17).

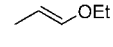
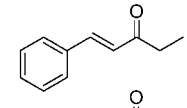
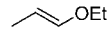
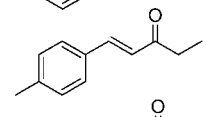
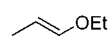
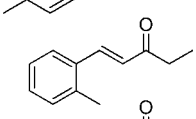
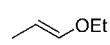
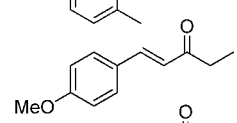
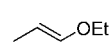
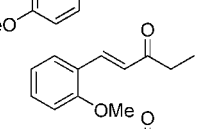
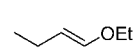
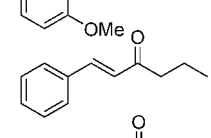
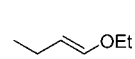
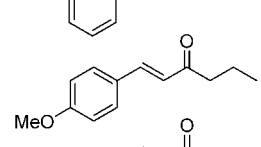
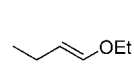
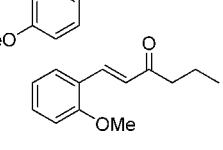
Because the reactions of substituted vinyl ethers were sluggish, it was decided to undertake a ligand screening. The results are shown in Table 3. Much to our surprise, the regioselectivity of the reaction was unaffected by the choice of ligand; be it monodentate or bidentate, the linear product was never detected, and only varying amounts of the homocoupling products were produced. Remarkably, the monophosphines significantly out-performed dppp, a ligand which has been universally used in regiocontrol of the Heck reaction of electron-rich olefins. Of the ligands tested, the bis(trifluoromethyl)-substituted PPh_3 (entry 4) and the hemilabile dpppO (entry 11) gave the best results, both affording ~95% conversion and complete α selectivity for the desired product.[21]

Encouraged by this success, we decided to continue the study of substituted vinyl ethers with dpppO as ligand, due to its lower cost and ease of availability compared to the monophosphine in entry 4.[22,23] In sharp contrast to dppp, dpppO allowed complete reactions of *p*-methoxy-β-bromostyrene with 1-propenyl and 1-butenyl ethyl ether in 0.75 and 4 h, respectively. The results from expanding the scope of this reaction are shown in Table 4. Good to excellent yields were obtained for a range of vinyl bromides in reaction times much shorter than those possible with the common dppp.

Lowering the quantity of catalysts, which are often based on expensive transition metals, is one of the main goals in making homogeneous catalysis greener and more economic. Hence, when we observed the higher activity of Pd−dpppO in the reaction of 2-substituted vinyl ethers, we decided to investigate if a lower catalyst loading in the reactions of other vinyl ethers would be feasible. Table 5 shows the results obtained with BVE and 2-hydroxyethyl vinyl ether. To our delight, the reactions at 1 mol % of Pd (entries 1−8) were complete in around 1 h and those with 0.1 mol % of Pd in 18 h (entries 9−11). For these reactions, the ligand to metal ratio was increased from 2 to 4; this appeared to be necessary for reproducibility at the reduced palladium loading. However, a lower yield was observed when *p*-methoxy-β-bromostyrene was coupled with BVE at the 0.1 mol % Pd loading (not shown). It was noticed previously that if the reaction mixture was allowed to stir overnight, the yield dropped from 82% to ca. 35% under the conditions of Table 2 (entry 3). This indicates that the initially formed diene from BVE and the methoxy-substituted β-bromostyrene is unstable under the chosen conditions, explaining the lower yield observed with BVE at the lower Pd loading where a longer reaction time was necessary. The ketal is seemingly much more stable under these conditions, with excellent yields being obtained for all substrates (Table 5, entries 9−11). These results compare

TABLE 4. Regioselective Heck Vinylation of 2-Substituted Vinyl Ethers[a]



Entry	Olefin	Product	t (h)	Yield (%)
1			1	91
2			1	76
3			0.75	79
4			1	77
5			0.75	90
6			5	86
7			4	77
8			4	80

[a] Reaction conditions: vinyl halide (1 mmol), vinyl ether (3 mmol), $Pd(OAc)_2$ (5 mol %), dppp (10 mol %), NEt_3 (3 mmol) in 2 mL of DMSO at 115 °C. Isolated yields given. No type **2** or homocoupling products were detected in the crude ^1H NMR.

(20) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 459.

(21) In the reaction where dppp was employed, ca. 10% of the ligand was oxidized to dppp oxide at 60% conversion, with the rest of the ligand coordinating to palladium according to ^{31}P NMR (a larger scale reaction was run to facilitate data collection). This suggests that the coupling reactions in Table 2 were catalyzed by Pd−dppp rather than Pd−dpppO species.

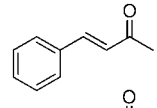
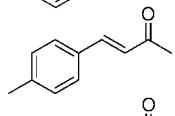
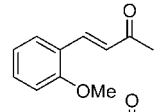
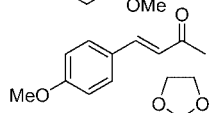
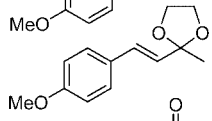
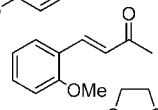
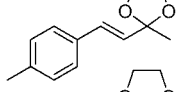
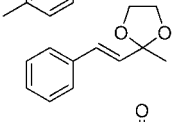
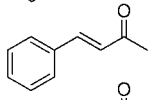
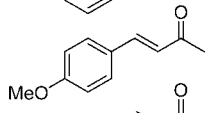
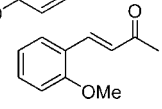
(22) (a) DpppO synthesis: Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831. Also see: (b) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241.

(23) Review on phosphine oxides: Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629.

(24) Review on the synthesis of α,β-unsaturated ketones: Foster, C. E.; Mackie, P. R. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, UK, 2005; Vol. 3, p 215.

(25) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303.

TABLE 5. Regioselective Heck Vinylation with Vinyl Bromides Using Pd−dpppO at Reduced Catalyst Loading[a]

Entry	Olefin	Product	t (h)	Yield (%)
1	O^nBu		1.25	84
2	O^nBu		1.25	97
3	O^nBu		1	90
4	O^nBu		1	92
5	$O(CH_2)_2OH$		1	92
6	$O(CH_2)_2OH$		1	88
7	$O(CH_2)_2OH$		1.25	82
8	$O(CH_2)_2OH$		1.25	95
9[b]	$O(CH_2)_2OH$		18	95
10[b]	$O(CH_2)_2OH$		18	93
11[b]	$O(CH_2)_2OH$		18	90

[a] Vinyl bromide (1 mmol), olefin (3 mmol), $Pd(OAc)_2$ (1 mol %), dpppO (4 mol %), and NEt_3 (3 mmol) in 2 mL of DMSO at 115 °C. [b] As footnote a but with $Pd(OAc)_2$ (0.1 mol %) and dpppO (0.4 mol %) and hydrolysis.

favorably with those shown in Table 2 and leave us with a highly selective and high-yielding protocol for the synthesis of (*E*)-α,*β*-unsaturated ketones as an alternative to other methods reported in the literature.[24−28]

Although we were pleased with the results thus far, they raised an important question: Is the ionic pathway **A** or the neutral pathway **B** responsible for the observed products? It is generally accepted that the α *arylation* of electron-rich olefins proceeds via a cationic mechanism (**A**, Scheme 1) and the related *vinylation* is judged under the same criteria, four of which exist in the literature. First, bidentate ligands are required to obtain branched products.[5] However, as revealed in the ligand screening, not only were bidentate ligands unnecessary for regiocontrol, the monodentate or hemilabile phosphines actually gave significantly faster rates. This is surprising as the neutral pathway

(26) Kim, J. H.; Lim, H. J.; Cheon, S. H. *Tetrahedron* **2003**, *59*, 7501.
(27) Yu, M.; Li, G.; Wang, S.; Zhanga, L. *Adv. Synth. Catal.* **2007**, *349*, 871.
(28) Yadav, J. S.; Subba Reddy, B. V.; Gupta, M. K.; Dash, U.; Pandey, S. K *Synlett* **2007**, 809.

TABLE 6. Effect of Halide Ions on the Vinylation of BVE with *p*-Methoxy-*β*-bromostyrene[a]

entry	additive[b] (%)	conv[c] (%)	selectivity[d]	conv[e] (%)	selectivity[d]
1	none	61	>99:1	61	>99:1
2	10	58	>99:1	32	>99:1
3	50	44	>99:1	12	>99:1
4	200	17	>99:1	<5	99:1

[a] Reaction conditions: *p*-methoxy-*β*-bromostyrene (1 mmol), BVE (3 mmol), $Pd(OAc)_2$ (3 mol %), dppp (6 mol %), and NEt_3 (3 mmol) in 2 mL of DMSO at 115 °C for 30 min. [b] NBu_4Br or NEt_4Cl. [c] NBu_4Br. [d] Molar ratio of **1**:**2**. [e] NEt_4Cl.

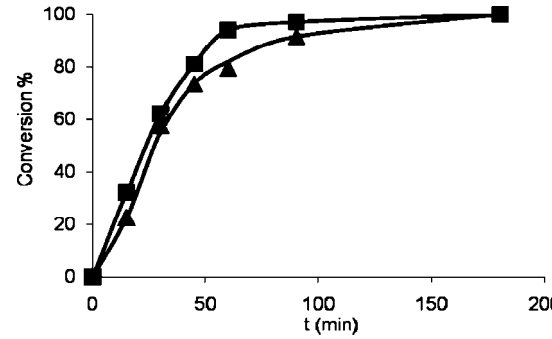


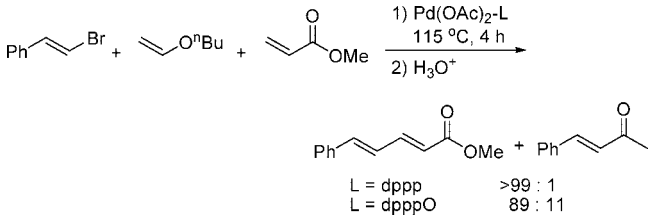
FIGURE 1. Reaction profiles of *cis*/*trans*-methoxy-*β*-bromostyrene reacting with BVE in DMSO: ■, *trans*; ▲, *cis*. Reaction conditions: 1 mmol of bromide, 3 mmol of BVE, 3 mol % of $Pd(OAc)_2$, 6 mol % of dppp, and 3 mmol of NEt_3 in DMSO at 115 °C.

B would become more likely under these conditions. Second, the addition of halide ions to reactions in which the pathway **A** is thought to dominate inhibits the catalysis.[5c,15e,f] This is particularly evident from arylation work done in this group, where addition of as little as 10 mol % of bromide halted the arylation of butyl vinyl ether.[15c] However, Table 6 shows that the vinylations in question are relatively insensitive to additional halide. Most notably, the reaction still proceeds in the presence of 200 mol % of NBu_4Br, *albeit* at a reduced rate. Addition of chloride ions retarded the reaction to a greater extent, although large quantities were required to completely inhibit the catalysis.

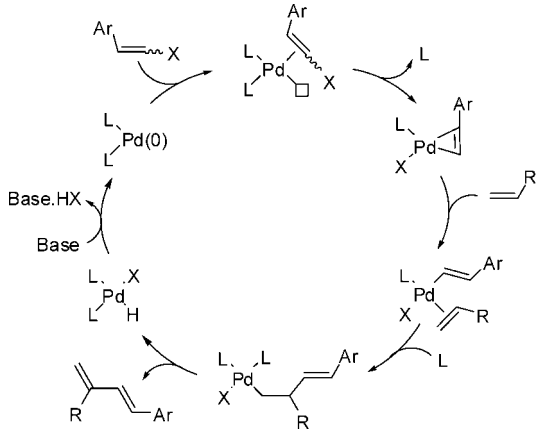
Third, the use of halide scavengers or ionic media enhances the selectivity and/or the rate of reactions where **A** is presumed to be the dominant pathway.[3a,5e,12,15c,e] We found that, contrary to arylation reactions, the vinylation was very slow in ionic liquids, and a negligible effect on the rate was observed in either [bmim][BF_4] or DMSO on addition of [$HNEt_3$][BF_4]. Finally, in a direct competition reaction between an electron-rich and an electron-deficient olefin, such as the one shown in Scheme 2, an electron-rich olefin would be more reactive when the pathway **A** is believed to prevail.[5a,15e] We found this was not the case when a reaction between a vinyl bromide and equimolar quantities of BVE and methyl acrylate was undertaken; regardless of the ligand chosen, *β*-vinylation of methyl acrylate was the dominant reaction (Scheme 2).

All of the results presented thus far were obtained with (*E*)-*β*-bromostyrenes. Further insight into the mechanism was gained by observations made with (*Z*)-*β*-bromostyrenes. The commercially available *β*-bromostyrene contains approximately 13% *cis* isomer, but interestingly, our products contained >99% *trans* olefins in all of the previously mentioned reactions. This prompted us to investigate the reactions of the *cis* isomer. Using the same conditions as those shown in Table 1 (entry 3), (*Z*)-*p*-methoxy-*β*-bromostyrene was reacted with BVE. Even with a starting material with an *Z*/*E* ratio of >19:1, the *E* isomer was

SCHEME 2. Competition Reaction between an Electron-Rich and -Deficient Olefin



SCHEME 3. Proposed Neutral Pathway for the Heck Vinylation of Electron-Rich Olefins



obtained exclusively according to NMR. This selectivity for the *trans* product may be attributed to a Pd-catalyzed isomerization during/after oxidative addition (vide infra).[29] The starting material does not appear to be isomerized before entering the catalytic cycle, as no change in the *cis*/*trans* ratio of the free vinyl halides was observed when they were subjected to the coupling reaction conditions in the absence of olefin.

The kinetic profiles of the two starting isomers reacting with BVE are shown in Figure 1, revealing an insignificant difference between them in rates. Amatore and Jutand showed that *cis*-vinyl bromides are significantly slower at oxidative addition than their *trans* counterparts.[30] Hence, the similarity in rates appears to rule out oxidative addition as rate determining in the Heck vinylation. As with arylation reactions, the vinylation under question might be rate-limited by the subsequent migratory insertion.[12b,15e]

The combination of all the pieces of evidence presented above leads us to believe that the regioselective internal vinylation of electron-rich olefins is more likely to proceed via the neutral pathway **B**. Hence, a modified mechanism for the reaction is proposed and shown in Scheme 3. Oxidative addition of the vinyl halide to a Pd(0) leads to an η^2 vinyl species. It is proposed that this proceeds via dissociation of a neutral ligand and η^2 coordination of the vinyl ligand. The incoming olefin then displaces the η^2 vinyl group, rendering it η^1 coordinating. Regardless of the geometry of the starting vinyl halide, the change in the coordination mode is expected to lead to a more stable *trans*-palladated olefin and, thus, the *trans* selectivity observed above. Alternatively, the isomerization could take place through a carbene species arising from the initial, η^1-coordinated vinyl oxidative-addition product.[29] The usual process of insertion, β-hydride elimination, and reductive elimination of HX then follows, regenerating the active Pd(0) catalyst and completing the catalytic cycle.

DFT calculations by Deeth and Brown have shown that for a vinyl group migrating to a vinyl ether, α-substitution is preferred even for a neutral Pd species.[10b] This is in agreement with our experimental findings. We note, however, the work of Amatore and Jutand, who showed that cationic [Pd(dppp)Ar(solvent)]$^+$ is more reactive toward olefins than the analogous [Pd(dppp)(Ar)X].[12b] They have also recently demonstrated that, for arylation in DMF, the insertion step always proceeds in an ionic fashion, i.e., from [ArPd(dppp)(DMF)]$^+$.[12a] Whether or not this is the case for the vinylation in DMSO remains to be investigated.

Conclusion

In summary, a highly efficient protocol for the Pd-catalyzed regioselective Heck vinylation of electron-rich olefins has been developed. The use of monodentate ligands and dpppO is the first example of these types of ligands being employed for regiocontrol in the Heck reaction. In particular, using dpppO as ligand enables reaction of more challenging olefins in short times, with lower Pd loadings being feasible. Together with the results concerning ionic liquid, halide inhibition, and the competition reaction, our findings indicate that the Heck α *vinylation* and α *arylation* may proceed via different pathways, with the former more likely to adopt the neutral pathway **B** (Scheme 1).

Experimental Section

General Procedure for the Heck Vinylation of Terminal Vinyl Ethers with a Pd−dppp Catalyst. An oven-dried, two-necked, round-bottom flask containing a stir bar was charged with Pd(OAc)$_2$ (0.03 mmol, 7 mg), dppp (0.06 mmol, 25 mg), β-bromostyrene (1 mmol, 183 mg, 0.12 mL), and 2 mL of DMSO. Following degassing three times, BVE (3 mmol, 301 mg, 0.4 mL) and NEt$_3$ (3 mmol, 303 mg, 0.4 mL) were injected sequentially. The flask was placed in a parallel reactor at 115 °C and stirred for an appropriate time. After the flask was cooled to room temperature, a small sample was taken for NMR analysis. Ten milliliters of 10% HCl was then added (except when 2-hydroxyethyl vinyl ether was used) and the solution extracted with 3 × 15 mL of DCM. The combined organic layers were washed to neutrality with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The α,β-unsaturated methyl ketone product (or cyclic ketal) was isolated from the crude mixture by chromatography on silica gel using ethyl acetate and hexane (1/99 to 10/90) as eluant. (*E*)-4-Phenylbut-3-en-2-one as an orange crystalline solid (141 mg, 96%): mp 38−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.56 (m, 3H), 7.50 (d, J = 16.0 Hz, 1H), 7.39−7.41 (m, 2H), 6.72 (d, J = 16.0 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 143.9, 134.8, 131.0, 129.4, 128.7, 127.6, 28.0; CI-MS *m*/*z* 147 [(M + H)$^+$, 100], 164 [(M + NH$_4$)$^+$, 51]; HRMS calcd for $C_{10}H_{11}O$ (M + H)$^+$ 147.0810, found 147.0813; IR ν (cm^{-1}) 1667, 1598, 1494. For details of other products, see Table 2 and the Supporting Information.

General Procedure for the Heck Vinylation of 2-Substituted Vinyl Ethers Using a Pd−dpppO Catalyst. An oven-dried, two-necked, round-bottom flask containing a stir bar was charged with Pd(OAc)$_2$ (0.03 mmol, 7 mg), dpppO (0.1 mmol, 52 mg), β-bromostyrene (1 mmol, 183 mg, 0.1 mL), and 2 mL of DMSO. Following degassing three times, NEt$_3$ (3 mmol, 303 mg, 0.4 mL) was injected, and the flask was placed in a parallel reactor at 115 °C. After 3−4 min, 1-propenyl ethyl ether (3 mmol, 258 mg, 0.3

(29) For an example of vinyl halide isomerization relevant to our mechanistic proposal, see: Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, *689*, 4642.

(30) Jutand, A.; Negri, S. *Organometallics* **2003**, *22*, 4229.

mL) was injected, and the mixture was stirred for an appropriate time. After being cooled to room temperature, a small sample was taken for NMR analysis. Ten milliliters of 10% HCl was then added and the solution extracted with 3 × 15 mL of DCM. The combined organic layers were washed to neutrality with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The α,β-unsaturated methyl ketone product was isolated from the crude mixture by chromatography on silica gel using ethyl acetate and hexane (1/99 to 5/95) as eluant. (*E*)-1-Phenylpent-1-en-3-one as a light orange oil (147 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 16.1 Hz, 1H), 7.50−7.54 (m, 2H), 7.37−7.39 (m, 3H), 6.74 (d, J = 16.1 Hz, 1H), 2.69 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 142.6, 135.1, 130.7, 129.3, 128.6, 126.5, 34.4, 8.6; CI-MS *m*/*z* 161 [$(M + H)^+$, 100], 178 [$(M + NH_4)^+$, 69]; HRMS calcd for $C_{11}H_{13}O$ $(M + H)^+$ 161.0966, found 161.0968; IR ν (cm^{-1}) 1698, 1600, 1492.

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Supporting Information Available: Typical experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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