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Dioxygen-Promoted Regioselective Oxidative Heck Arylations of Electron-Rich Olefins with Arylboronic Acids

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Arylations of electron-rich heteroatom-substituted olefins were performed with arylboronic acids. This appears to constitute the first example of palladium(II)-catalyzed internal Heck arylations. The novel protocol exploits oxygen gas for environmentally benign reoxidation and a stable 1,10-phenanthroline bidentate ligand to promote the palladium(II) regeneration and to control the regioselectivity. Internal arylation is strongly favored with electron-rich arylboronic acids. DFT calculations support a charge-driven selectivity rationale, where phenyls substituted with electron-donating groups prefer the electron-poor α-carbon of the olefin. Experiments, verified by calculations, confirm the cationic nature of the catalytic route. This Heck methodology provides a facile and mild access to functionalized enamides. Controlled microwave heating and increased oxygen pressure were used to further reduce the reaction time to 1 h.

Introduction

Control of regioselectivity is a fundamental feature of organic synthesis, yet it is still a challenge to direct the regioisomeric outcome of many transition-metal-catalyzed processes. Among these reactions, the intermolecular palladium-catalyzed Heck coupling has emerged as one of the most efficient and reliable methods for carbon−carbon bond formation.[1−3] The reaction provides attractive features for preparative chemistry because of high chemoselectivity and promising possibilities to control regio- and stereoselectivity.[4]

In Heck arylation chemistry, generation of the starting arylpalladium(II) intermediate may be accomplished by three different methods: (a) from a palladium(0) species and an aryl halide (or pseudo-halide) via oxidative addition, (b) from a palladium(II) center and an organometallic reagent by transmetalation, or finally (c) from a palladium(II) salt and an arene via electrophilic palladation.[5] The last two protocols require a palladium(0) oxidant to become catalytic in palladium. Therefore, the Pd(0) self-regenerating oxidative addition route (a) is so far the most commonly employed. Despite this, the recent development of new, convenient, and nontoxic arylpalladium precursors has given transmetalation approach b new generality.[6−11] Especially arylboronic acids offer several advantages as transmetalation substrates because of the large commercial availability, the stability to moisture and air, the low toxicity, and the easy removal of boron-derived byproducts unlike those of other organometalloids.

A substantial improvement of the palladium(II)-catalyzed transmetalation methodology, from both preparative and environmental points of view, was the use of molecular oxygen as the sole reoxidant of reluctant palladium(0).[12−14] The power of this oxidative procedure was recently demonstrated in smooth terminal Heck couplings of organoboron compounds with different olefins.[15,16]

Exploiting palladium(0)-based oxidative addition method a, regioselective Heck arylations of the internal α-carbon of electron-rich acyclic enamides and vinyl ethers are achievable with aryl triflates using appropriate phos-

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phine or nitrogen bidentate ligands.[17] By using these bifunctional ligands, the coordination of the double bond occurs via dissociation of the weakly coordinating triflate anion, affording a cationic π-complex that favors electronically controlled internal insertion. Alternatively, aryl bromides or iodides can replace the aryl triflates when stoichiometric amounts of halide sequestering silver(I) or thallium(I) salts are added.[17] The drawbacks of these delicate methods to perform "cationic" Heck reactions are that aryl triflates are rarely commercially available and that the metal additives are either expensive or very toxic. Promisingly, new methods have recently been reported that afford the same high regiochemical selectivity with organic bromides by increasing the polarity of the reaction system,[18,19] or by increasing the bidentate ligand/palladium ratio.[20]

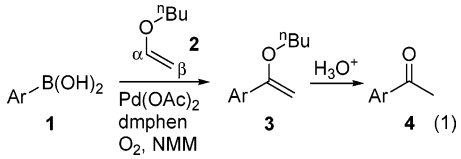
The presented background suggested to us that arenes substituted with non-metal-coordinating electropositive transmetalation handles (e.g., $-B(OH)_2$) should provide a new oxidative gateway into the cationic manifold, enabling internal arylations of nonfunctionalized enamides and enol ethers. Furthermore, the employment of inexpensive, nontoxic chelating nitrogen ligands to both control selectivity and facilitate efficient redox cycling between palladium(0) and palladium(II) using dioxygen would be advantageous.[21,22]

Inspired by the pioneering work with aryl triflates by Cabri et al.,[23,24] we recently discovered that highly efficient terminal Pd(II)-catalyzed Heck arylations with electron-poor olefins are feasible when palladium acetate and rigid, oxidatively stable 2,9-dimethyl-1,10-phenanthroline (dmphen) ligand are used.[16] We herein report that oxygen-promoted and regioselective α-arylations of enamides can be efficiently performed with arylboronic acids as starting materials using a dmphen-ligated palladium(II) catalyst. Complementary DFT calculations provide an explanation for the experimental outcome with respect to activity and selectivity. Also, theory supports a catalytic route mediated by cationic Pd(II) species.

Results

Experimental Results. The first series of experiments demonstrated that palladium(II)-catalyzed arylations of butyl vinyl ether (**2**) with phenylboronic acid (**1f**) could be performed under an oxygen balloon atmosphere using the planar dmphen ligand, palladium acetate, and *N*-methylmorpholine (NMM) as base (eq 1 and Table 1). Due to the general instability of α-arylated vinyl ethers **3**,[25,26] the products were in all cases isolated after acidic hydrolysis as the corresponding methyl ketones **4**. The

TABLE 1. Validation of the Oxidative Protocol for Internal Arylation of 2[a]



entry	$ArB(OH)_2$		solvent	internal product	α:β[b] (**3**)	yield[c] (%)
1	Ph	**1f**	DMSO	**3f**	78:22	<5
2	Ph	**1f**	MeCN	**3f**	91:9	12
3	Ph	**1f**	EtCN	**3f**	91:9	17
4	Ph	**1f**	dioxane	**3f**	95:5	48
5	Ph	**1f**	dioxane	**3f**	97:3	46[d]
6	Ph	**1f**	dioxane	**3f**	96:4	51[e,f]
7	Ph	**1f**	dioxane	**3f**	27:73	<5[g]
8	Ph	**1f**	dioxane	**3f**	22:78	<5[h]
9	4-PhO-Ph	**1c**	dioxane	**3c**	99:1	59[f,i]
10	2-naphthyl	**1g**	dioxane	**3g**	93:7	53[f,j]

[a] The reactions were performed with $ArB(OH)_2$ (1.0 mmol), *n*-butyl vinyl ether (3.0 equiv), NMM (2.0 equiv), $Pd(OAc)_2$ (0.020 equiv), and dmphen (0.024 equiv) in solvent (2.5 mL) at 35 °C under O_2 (balloon) for 18 h, >95% conversion of **1**. [b] Determined by GC−MS and ^{1}H NMR. [c] GC−MS yield of acetophenone (**4f**) obtained after hydrolysis of **3f** with HCl(aq). [d] $Pd(OAc)_2$:dmphen = 0.020:0.048. [e] $Pd(OAc)_2$:dmphen = 0.040:0.048. [f] Isolated yield, >95% pure **4c**,**f**,**g** according to GC−MS. [g] No dmphen. [h] LiCl as additive (5.0 equiv). [i] 50 °C. [j] 25 °C.

presence of chelating dmphen not only provided a catalytic Pd(II)-species that afforded high internal product selectivity but also facilitated an efficient palladium redox cycling in dioxane (entries 4−6). It is worth noting that the initial transmetalation process occurred smoothly with the conformationally restricted dmphen ligand despite the low reaction temperature (35 °C) and that the catalyst performance was good, resulting in the full conversion of **1f** (entries 4−6). The moderate yields of arylated enol ether **3** in Table 1 were due to the use of arylboronic acid **1** as the limiting reactant, the latter being susceptible to competing hydrodeboronation and aryl−aryl homocoupling. Interestingly, the polarity of the solvents greatly influenced the conversion, yield, and regioselectivity, and it was found that use of less polar solvents increased regioselectivity (compare entries 1−3 with entries 4−6). The reaction condition was further fine-tuned in dioxane with respect to the amount of palladium acetate (4.0%) and dmphen (4.8%) to provide a maximum isolated yield of 51% for **3f** with an α:β-selectivity of 96:4 (entry 6). Omission of the dinitrogen ligand, or addition of stoichiometric amounts of LiCl, caused the destruction of the regiocontrol and also reduced the rate of the reaction (entries 7 and 8). Alternative Pd(II) reoxidants such as TMANO or Ag_2CO_3 afforded no detectable productivity. In contrast to internal palladium(0)-catalyzed couplings with aryl triflates,[26] bidentate phosphine ligands provided incomplete conversion in our oxidative protocol. Phosphine ligands have also been reported by other groups to afford low reactivity in direct vinylations of arylboronic acids.[27] In conflict with

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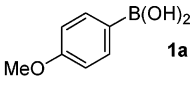
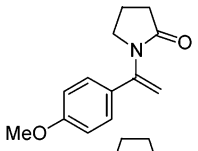
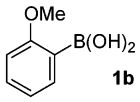
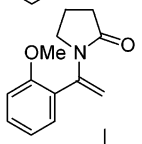
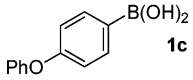
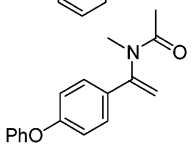
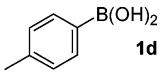
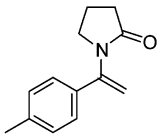
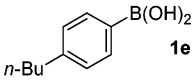
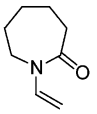
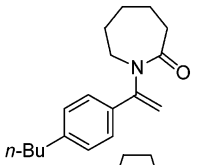
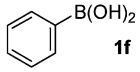
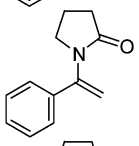
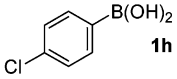
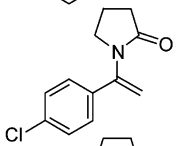
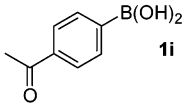
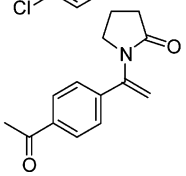
TABLE 2. Presentation of the Oxidative Protocol for Internal Arylation of Enamides 5−7[a]

Entry	$ArB(OH)_2$	Olefin	Internal Product	α/β[b]	Isolated Yield of **8-10** [or **4**] (%)[c]
1	 **1a**	 **5**	 **8a**	99/1	79
2	 **1b**	**5**	 **8b**	99/1	51(**4b**)[d]
3	 **1c**	 **6**	 **9c**	99/1	60
4	 **1d**	**5**	 **8d**	99/1 (54/46)[e]	96 (<10)[e]
5	 **1e**	 **7**	 **10e**	96/4	89[f]
6	 **1f**	**5**	 **8f**	94/6	80 (**4f**)[f]
7	 **1h**	**5**	 **8h**	92/8	31 (**4h**)[f]
8	 **1i**	**5**	 **8i**	95/5	40 (**4i**)[f]

[a] The reactions were performed with $ArB(OH)_2$ (2.0 equiv), enamide (1.0 mmol), NMM (2.0 equiv), $Pd(OAc)_2$ (0.020 equiv), and dmphen (0.024 equiv) in 1,4-dioxane (2.5 mL) at 50 °C under O_2 (balloon) for 18 h. [b] Determined by GC−MS and ^{1}H NMR. [c] Isolated yield, >95% pure **8**−**10** or **4** according to GC−MS. Methyl ketone **4** was obtained after hydrolysis of **8** with HCl(aq). [d] 80 °C. [e] The reaction was performed at 70 °C for 28 h with LiCl (5 equiv). The yield was measured by GC−MS using naphthalene as internal standard (less than 22% conversion of **5**). [f] $Pd(OAc)_2$:dmphen = 0.040:0.048.

the report by Jung, arylation of **2** with **1f** employing ligandless conditions, Na_2CO_3, and DMF did not, in our laboratory, afford a selective terminal arylation but rather a mixture of the α- and β-isomers (α:β = 27:73).[15]

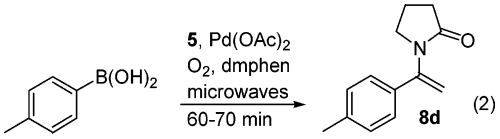
The oxidative procedure was also successfully extended to the internal vinylation of electron-rich boronic acids **1c**,**g**, giving results similar to those of parent **1f**, although using only a low catalyst loading (2% palladium acetate and 2.4% dmphen, entries 9 and 10). Vinylation of electron-deficient 3-acetylphenylboronic acid resulted in a highly regioselective but low-yielding reaction.

Having identified an appropriate protocol with **2** (entry 4, Table 1), the selective transformation was successfully extended to the arylation of enamides **5**−**7** employing a set of different arylboronic acids (Table 2). Further optimization of yield with regard to catalyst concentration and temperature was carried out in entries 2 and 5−8. With this class of olefins the yields were improved by the reversal of the reaction stoichiometry (enamide:boronic acid = 1:2), while the high regioselectivity was not greatly affected by the diverse *N*-substitutions of **5**−**7**. Arylated **8f**,**h**,**i** were isolated as the corresponding methyl ketones for purification reasons, while Heck product **8b** underwent competing hydrolysis to **4b** directly during the arylation reaction.[28] It is notable that all reactions ran well using mild conditions, i.e., a weak base and low temperature (50 °C), with the exception of the sterically hindered **1b** (entry 2, Table 2), which required an elevated temperature (80 °C). Addition of LiCl to the reaction in entry 4 resulted in a slow and nonselective arylation of **5**. The general trend was that arylboronic acids substituted with electron-donating groups (EDGs)

were the best substrates, affording both the highest internal regioselectivities (α:β > 99:1) and yields without generating any significant byproducts. The electron-poor arylboronic acids **1h**,**i** furnished depressed yields (31−40%), yet satisfactory selectivities, accompanied by competing biphenyl formation (entries 7 and 8). Interestingly, **1i** was completely inert to butyl acrylate under neutral conditions.[16] Other investigated arylboronic acids, with electron-withdrawing 4-CF_3, 4-CN, 4-Br, and 4-CHO phenyl substituents, also failed to undergo significant conversions, and instead the corresponding biaryl derivatives were the major products.

Controlled microwave heating is well-known to speed up nongaseous metal-catalyzed organic transformations.[29,30] In contrast, the use of reactive gases under microwave irradiation has not been thoroughly investigated. This is probably a consequence of the utilization of single-mode applicators that typically only allow processing of small and sealed reaction volumes.[31−33] In microwave-assisted oxygen gas promoted chemistry, the reaction vessel must be either (a) large enough to accommodate the necessary gas volume under pressurized conditions or (b) equipped with a sophisticated inlet system for a continuous supply of oxygen. To expand the scope of the presented selective but slow Heck methodology, we here report on microwave-heated oxidative Heck arylations in two different types of batch reactors following these two strategies.[34]

The arylation of enamide **5** with **1d** was chosen as a typical dmphen-controlled oxidative Heck reaction, and propionitrile was selected as the reaction medium mainly because of the superior microwave-absorbing properties of nitrile solvents compared to microwave-transparent 1,4-dioxane (eq 2).[34−36]



1d 100 °C, 1 mmol-scale: α/β = 93/7, 80% (**8d**)
80 °C, 10 mmol-scale: α/β = 97/3, 66% (**4d**)

Initially, the protocol was investigated on a 1 mmol scale. The 25 mL sealed borosilicate vessel containing the reaction mixture was first prepressurized with oxygen (∼3 bar) and then heated in a single-mode microwave synthesizer. After several different reaction parameters were explored, it was found that the reaction time could be reduced to 1 h at 100 °C with 5 mol % palladium loading, though at the expense of a slight decrease of selectivity and isolated yield of **8d** (α:β = 93:7, 80%). As a further development step, the microwave reaction was performed on a multigram scale (10 mmol) in a multimode autoclave reactor using a continuous flow of oxygen and a lower reaction temperature (eq 2). In this 80 °C, 70 min process, only a minor reduction of the α:β-selectivity to 97:3 was encountered (reduced from 99:1 at 50 °C, Table 2, entry 4). Both microwave reactions were safely executed without any special precautions.

Computational Results. DFT calculations at the B3LYP level of theory were performed for the regioselectivity-determining insertion step following a cationic pathway. Five different arylboronic acids, equipped with functional groups in the *para*-position, were inserted into the cyclic enamide **5**. Results of calculations and experiments were subsequently compared with respect to activity and selectivity. Computational details as well as the energies and Cartesian coordinates of all investigated structures are presented in the Supporting Information.

A somewhat reduced cationic Pd(II)−diimine model of the actual catalyst species was used to make the computations feasible. Thus, the chelating dmphen was represented by an *N*,*N*-dimethyl-1,2-ethanediimine ligand. Previous investigations on related Heck systems have shown that such comparatively small diimine models perform well when trends in activity and selectivity are mapped out.[37,38] The inserting enamide **5** and the *para*-substituted phenyls were fully represented, as schematically presented in Scheme 1. The resting state prior to insertion is the π-complex **B**, where the enamide is coordinated with the carbon−carbon double bond perpendicular to the ligand plane of the metal (Figure 1). Following the π-coordination, the olefin rotates clockwise or counterclockwise into the ligand plane, forming the transition-state geometry $\mathbf{TS}_\alpha$ or $\mathbf{TS}_\beta$, respectively (Figure 1). The regioselectivity is thus determined by the energy difference of the two possible transition-state structures, and the insertion barrier is calculated as the difference between transition-state and π-complex energies. In addition to the energies of the stationary points, selected orbital stabilities and atomic charges were also calculated. Table 3 summarizes the computational results.

Discussion

Correlating the experimental and theoretical results at hand allows for rationalization of trends observed with respect to activity and selectivity as a function of the electronic properties of the arylboronic acids. The phenyl *para*-substituents in Table 3 are arranged from electron-donating (EDGs) to electron-withdrawing (EWGs) groups. From the theoretical results it can be concluded that the exothermicity of π-complex formation increases with the electron-withdrawing character of the phenyl substituent. This agrees with the fact that the EWGs stabilize the

(28) The isolation of **4f**,**h**,**i** instead of enamides **8f**,**h**,**i** were performed because of difficulties in separating **8f**,**h**,**i** from the corresponding terminal isomers using flash chromatography. The internally arylated enamides **8f**,**h**,**i** could, however, be easily purified up to ∼90% purity without hydrolysis. Heck product **8b** probably underwent direct hydrolysis due to the high reaction temperature (80 °C).

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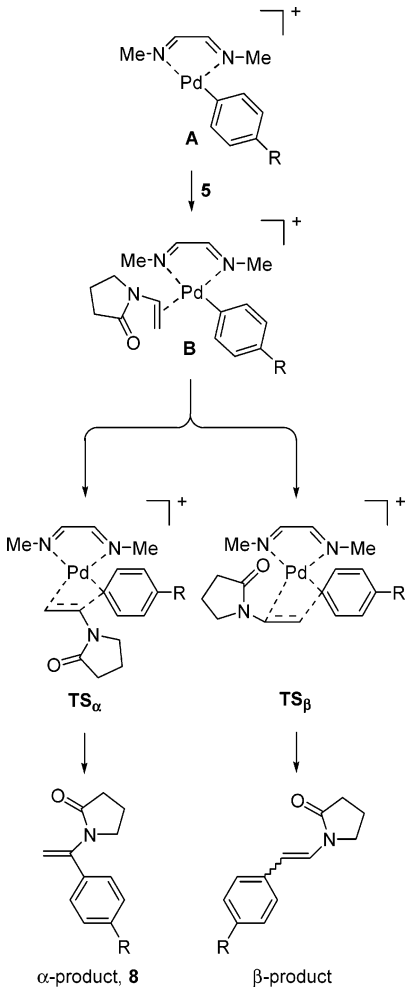
SCHEME 1. Regiodetermining Insertion of 5



unoccupied MO of the metal in the cationic oxidative addition complex **A (**Scheme 1), accepting electrons donated from the olefin. For example, the accepting MO of **A** lies 0.5 eV lower for R = −COMe (−7.0 eV) than for R = −OMe (−6.5 eV). Furthermore, calculations show that arylboronic acids with EDGs have lower insertion barriers, in parallel with weaker π-complexation energies (Table 3). This is consistent with a considerable part of the π-coordination being lost in reaching the transition state (see Figure 1).[37] The theoretical trend is supported by experiments, where isolated yields with electron-deficient arylboronic acids such as **1h** and **1i** (Table 2) are low (as well as for boronic acids with 4-CF_3, 4-CN, 4-Br, and 4-CHO aryl substituents, not listed in Table 2) compared to those with electron-rich species such as **1a** and **1d**.

A clear trend in selectivity is also observed, where EDGs on the phenyl ring provide excellent selectivity in favor of the α-product (Table 2). With increasing electron-withdrawing character of the phenyl *para*-substituent, α-selectivity is reduced. In the series of insertions modeled by calculations, only the *para*-substituent on the phenyl ring changes from case to case. Since these groups are sterically undemanding and do not interfere with the olefin during insertion, it is reasonable to attribute this selectivity trend to electronic effects. Such electronic influences can be due to both orbital and charge contributions. Investigating these possibilities further, relevant electronic properties of the inserting enamide **5** were calculated. The difference between the π*-orbital coefficients ($2p_z$) of the C=C double bond turned out to be very small (0.02), ruling out significant orbital-driven selectivity effects. However, the charge separation between the two carbons was notable (0.3 electron), with the terminal carbon being the more negatively charged. Table 3 lists the charge of the *ipso*-carbon of the phenyl ring for the different species **A**, the carbon that will attack either of the olefin carbons. Charge differences are rather small, but the largest difference is seen when the 4-OMe-substituted phenyl is compared with the 4-COMe-substituted phenyl, with the electron-donating methoxy group giving the most negatively charged *ipso*-carbon (entries 1 and 5, Table 3).[39] Charge-driven regioselectivity thus represents a reasonable explanation of the high degree of internal arylation observed in the investigated dmphen-controlled Heck processes.

Previous theoretical work has disclosed significant differences in both activity and selectivity between cationic and neutral Pd(II) intermediates in Heck couplings of neutral or electron-rich olefins. For propene inserting into the phenyl−palladium bond, it was found that neutral Pd(II) species had an increased reaction barrier compared to cationic Pd(II) complexes. This increase in barrier corresponded to a diminished thermodynamic driving force for the insertion step. Furthermore, the direction of the insertion was shifted toward reduced α-product formation.[40]

To verify the cationic route for the presented oxidative arylations, a neutral arylpalladium(II) catalyst was also investigated both experimentally and theoretically. In the experimental preparation of **8d** (entry 4, Table 2), LiCl was added, which made the reaction very sluggish (<22% conversion of **5** after 28 h at 70 °C). The regioselectivity was also destroyed, resulting in an α/β-isomeric mixture of 54:46. Calculations provide the optimized structure of the neutral π-complex **B′**, as shown in Figure 2. Chlorine positions itself trans to the phenyl ring, displacing one of the imine coordinations to palladium. Calculating the structures and energies of the corresponding neutral **TS′**$_\alpha$ and **TS′**$_\beta$ produced the insertion barrier and regioselectivity for the inserting enamide **5**.

The reaction barrier for α-product formation was calculated to be $\Delta E_\alpha^* = 25.3$ kcal/mol, i.e., significantly higher than for the parallel cationic case, $\Delta E_\alpha^* = 12.4$ kcal/mol (entry 2, Table 3). This gives a plausible explanation for the low conversion encountered with LiCl as additive even at the elevated temperature of 70 °C (entry 4, Table 2). A relative decrease in α-selectivity was also found, with $\Delta\Delta E^* = -0.5$ kcal/mol in the neutral case, compared to $\Delta\Delta E^* = -2.4$ kcal/mol for the cationic system. Thus, the theoretical predictions and the experimental results are in pleasing agreement, strongly supporting the idea of a cationic catalytic route.

Conclusion

We propose that the presented regioselective oxidative Heck arylation of acyclic enamides proceeds via a cationic

(39) A charge of +0.16 au was calculated for 4-CN-substituted complex **A**. However, as noted in the Results, the very low yield of arylated product for this and other electron-poor arylboronic acids prevented the reliable evaluation of the regioselectivity.

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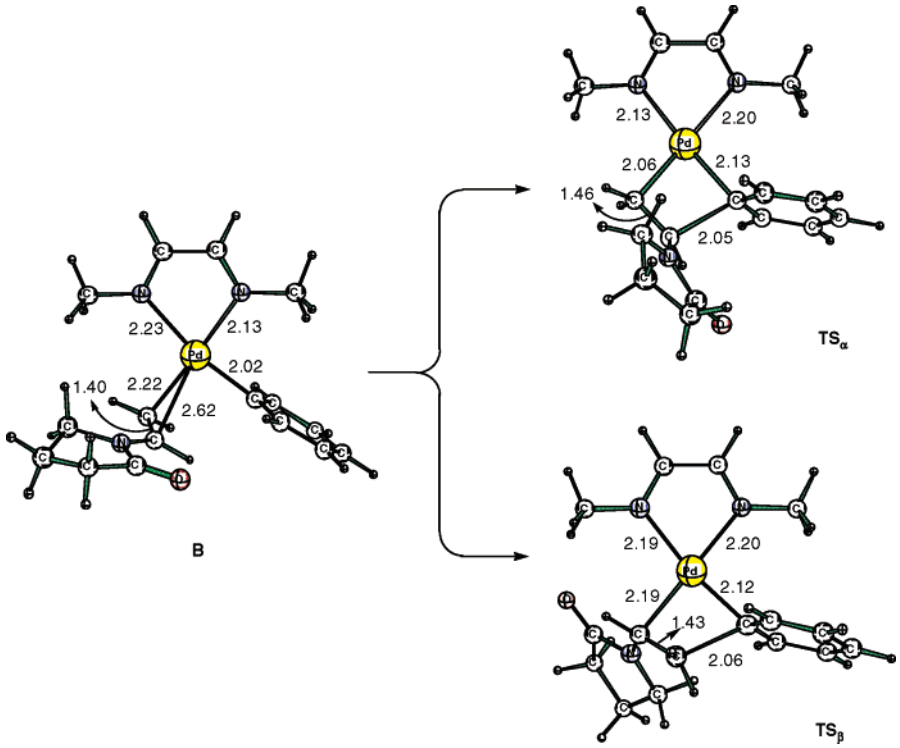

FIGURE 1. Representative structures of the cationic π-coordinated olefin species and the two possible transition-state structures **TS**$_\alpha$ and **TS**$_\beta$.

TABLE 3. Computational Results of the Migratory Insertion of 5 with Selected *para*-Substituted Cationic Arylpalladium(II) Diimines

entry	*para*-substituent (R)	ΔE_π[a]	ΔE_α*[b]	ΔE_β*[c]	$\Delta\Delta E$*[d]	acc MO[e]	charge[f]	d_{Pd-C}[g]
1	−OMe	−27.5	9.8	13.5	−3.7	−6.5	−0.13	1.923
2	−Me	−27.9	12.4	14.8	−2.4	−6.7	−0.03	1.972
3	−H	−29.0	13.9	15.3	−1.4	−6.8	+0.08	1.975
4	$-CF_3$	−30.8	15.3	16.4	−1.1	−7.2	−0.02	1.976
5	−COMe	−31.2	15.9	16.4	−0.5	−7.0	+0.09	1.977

[a] π-Complexation energy (kcal/mol). [b] Reaction barrier for insertion forming the α-product **8** (kcal/mol). [c] Reaction barrier for insertion forming the β-product (kcal/mol). [d] $\Delta\Delta E^* = \Delta E_\alpha^* - \Delta E_\beta^*$ (kcal/mol). [e] Energy of the accepting MO of **A** (the LUMO + 1, a 5s4d hybrid) (eV). [f] Partial atomic charge of the *ipso*-carbon of **A** (au). [g] Distance between the *ipso*-carbon and Pd of **A** (Å).

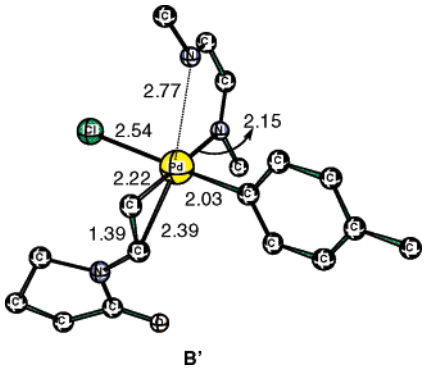

FIGURE 2. Neutral Pd(II) π-complex after the addition of LiCl (hydrogens left out for clarity).

π-complex stabilized by a chelating phenanthroline ligand. DFT studies provide a rational insight into the origin of regiocontrol influenced by the electronic character of arylboronic acids. The dmphen ligand not only controls the internal regioselectivity, but also mediates a cost-efficient reoxidation of reluctant palladium(0) with dioxygen, allowing a low catalyst loading. In addition, the first examples of microwave protocols with successful employment of oxygen gas as an efficient palladium(0) reoxidant are reported. Finally, the simple procedure, good functional group tolerance, and availability of the arylboronic acids make the procedure a valuable complement to the established use of aryl triflates and aryl bromides for the direct Heck preparation of acetophenones and α-aryl enamides.

Experimental Section

General Procedure for Arylation of *n*-Butyl Vinyl Ether (2) and Isolation of 4, Table 1. A mixture of $Pd(OAc)_2$ (0.020 or 0.040 mmol) and 2,9-dimethyl-1,10-phenanthroline (0.024 or 0.048 mmol) in 1,4-dioxane (0.5 mL) was stirred for 15 min at 50 °C (see Table 1 for further details regarding catalyst amount). To this suspension, which had turned yellow, were successively added arylboronic acid (1.0 mmol), *N*-methylmorpholine (0.22 mL, 2.0 mmol), *n*-butyl vinyl ether (3.0 mmol), and 1,4-dioxane (2.0 mL). The oxygen-filled balloon was then attached atop and the mixture vigorously stirred at the specified temperature and time. After cooling to room temperature, the balloon was removed and the mixture diluted

with HCl (5 M, 2 mL) for 1 h and subsequently partitioned between ethyl acetate and H_2O. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product, which was purified by centrifugal chromatography (ethyl acetate in hexane, silica gel 60) or bulb-to-bulb distillation to afford the pure product **4**.

General Protocol for Internal Arylation of Acyclic Enamides and Isolation of 8−10, Table 2. A mixture of $Pd(OAc)_2$ (0.020 or 0.040 mmol) and 2,9-dimethyl-1,10-phenanthroline (0.024 or 0.048 mmol) in 1,4-dioxane (0.5 mL) was stirred for 15 min at 50 °C in a round-bottomed flask. To this suspension, which had turned yellow, were successively added arylboronic acid (2.0 mmol), *N*-methylmorpholine (0.22 mL, 2.0 mmol), enamide **5**, **6**, or **7** (1.0 mmol), and 1,4-dioxane (2.0 mL). The oxygen-filled balloon was then attached atop and the mixture vigorously stirred at the specified temperature and time. After cooling to room temperature, the balloon was removed, the mixture was diluted with water and ethyl acetate, and the contents were transferred into a separatory funnel. The flask was washed further with ethyl acetate. After the addition of more ethyl acetate and water, the layers were separated. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by centrifugal chromatography using hexane or a mixture of hexane and ethyl acetate as eluent to afford the pure enamide product.

General Procedure for Arylation of Enamides 5−7 and Isolation of 4, Table 2. A mixture of $Pd(OAc)_2$ (0.020 or 0.040 mmol) and 2,9-dimethyl-1,10-phenanthroline (0.024 or 0.048 mmol) in 1,4-dioxane (0.5 mL) was stirred for 15 min at 50 °C (see Table 2 for further details regarding amount of catalyst and temperature). To this suspension, which had turned yellow, were successively added arylboronic acid (2.0 mmol), *N*-methylmorpholine (0.22 mL, 2.0 mmol), enamide **5**, **6**, or **7** (1.0 mmol), and 1,4-dioxane (2.0 mL). The oxygen-filled balloon was then attached atop and the mixture vigorously stirred at the specified temperature and time. After cooling to room temperature, the balloon was removed and the mixture diluted with HCl (5 M, 2 mL) for 1 h and subsequently partitioned between ethyl acetate and H_2O. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product, which was purified by centrifugal chromatography (ethyl acetate in hexane, silica gel 60) or bulb-to-bulb distillation to afford the pure product **4**.

***N*-(1-[4-Methoxyphenyl]ethenyl)-2-pyrrolidinone (8a)**. The residue was purified by centrifugal chromatography (silica gel 60, 50% ethyl acetate in hexane) to afford the title product as a colorless liquid (0.171 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (m, 2H), 2.56 (t, 2H, J = 8.1 Hz), 3.54 (t, 2H, J = 7.0 Hz), 3.81 (s, 3H), 6.86 (m, 2H), 6.86 (m, 2H), 7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 31.9, 49.6, 55.3, 108.0, 113.8, 127.6, 128.6, 143.1, 159.8, 174.6. (IR, $CDCl_3$): 1701 cm^{-1}. MS: *m*/*z* (relative intensity) 217 (M^+, 100), 174 (58), 133 (21). HRMS (FAB+): *m*/*z* calcd for $\{C_{13}H_{15}NO_2\}$ 217.1103, found 217.1103

Microwave Experiments. (A) Small Scale in a Single-Mode Reactor. A mixture of $Pd(OAc)_2$ (0.011 g, 0.050 mmol) and dmphen (0.022 g, 0.100 mmol) in EtCN (1.0 mL) was stirred for 10 min (color change from brown to yellow), and the yellow suspension was transferred into a Smith vial (32 mL) containing 4-methylphenylboronic acid (**1d**; 0.28 g, 2.0 mmol), *N*-vinylpyrrolidinone (**5**; 0.11 g, 1.0 mmol), and *N*-methylmorpholine (0.22 mL, 2.0 mmol) in EtCN (7.0 mL). The vial was flushed with oxygen gas, capped, and then pressurized with oxygen gas through a sharp needle attached to the oxygen cylinder tube (ca. 3 bar on the basis of the pressure gauge readings of the oxygen cylinder). The vial was then heated at 100 °C for 1 h in the microwave synthesizer, cooled to room temperature, and uncapped. The reaction mixture was thereafter partitioned between ethyl acetate and H_2O. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product, which was purified by centrifugal chromatography (20% ethyl acetate in hexane, silica gel 60) to afford the pure product **8d** as a light-yellow oil (0.161 g, 80%).

(B) Large Scale in a Multiple-Mode Microwave Batch Reactor. A mixture of $Pd(OAc)_2$ (0.112 g, 0.500 mmol) and dmphen (0.217 g, 1.00 mmol) in EtCN (5.0 mL) was stirred for 10 min (color change from brown to yellow) and subsequently transferred into a Teflon vessel (350 mL) containing **1d** (2.8 g, 20 mmol), **5** (1.10 g, 10 mmol), and *N*-methylmorpholine (2.2 mL, 20 mmol) in EtCN (75 mL). The vessel was attached to the flange, the autoclave was closed, and oxygen was supplied through the gas inlet from the oxygen cylinder. The oxygen pressure was maintained at ca. 3 bar throughout, while the temperature was monitored by a fiber-optic thermometer inserted inside the reactor vessel. The stirring reaction mixture was then heated at 80 °C for 70 min in the microwave synthesizer (Emrys Advancer), and thereafter cooled to room temperature. The autoclave was opened, and the reaction mixture was stirred with dilute HCl (5 M, 30 mL) for 1 h. The reaction mixture was subsequently partitioned between ethyl acetate (250 mL) and H_2O (250 mL). The organic layer was separated, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product, which was purified by centrifugal chromatography (2% ethyl acetate in hexane, silica gel 60) to afford the pure ketone **4d** as a light-yellow oil (0.885 g, 66%).

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, computational details, and energies and Cartesian coordinates of all investigated structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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