JOC Article

Selective Terminal Heck Arylation of Vinyl Ethers with Aryl Chlorides: A Combined Experimental−Computational Approach Including Synthesis of Betaxolol

Gopal K. Datta, Henrik von Schenck, Anders Hallberg, and Mats Larhed*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala University, BMC, Box-574, SE-751 23 Uppsala, Sweden

mats@orgfarm.uu.se

Received February 6, 2006

Reaction conditions have been developed for palladium-catalyzed terminal (β-) arylation of acyclic vinyl ethers with high regioselectivity using inexpensive aryl chlorides as starting materials and the P(t-Bu)$_3$ releasing preligand [(t-Bu$_3$)PH]BF$_4$ as the key additive. This swift and straightforward protocol exploits non-inert conditions and controlled microwave heating to minimize handling and processing times and uses aqueous DMF or environmentally friendly PEG-200 as the reaction medium. The selectivity for linear β-product in PEG-200 is slightly higher than in aqueous DMF. DFT calculations support a ligand-driven selectivity rationale, where the electronic and steric influence of bulky P(t-Bu)$_3$ ligand provides improved β-selectivity in the essential insertion step also with electron-rich aryl chlorides. A tentative computational rationalization of the improved selectivity in non-methylated PEG is discussed. Finally the synthetic methodology was used to provide efficient access to linear p-[2-(cyclopropylmethoxy)-ethyl] phenol from p-nitrophenyl chloride, a key intermediate in the synthesis of the β-adrenergic blocking agent Betaxolol.

Introduction

The Heck reaction is an excellent palladium(0)-catalyzed method to introduce an aromatic group to one end of a double bond.[1−3] Using aryl halides or sulfonate esters as arylpalladium precursors, many impressive examples of both inter- and intramolecular Heck applications have been published.[4] When this vinylic substitution reaction is applied to acyclic electron-poor olefins, the terminal (β-) product is obtained as an E/Z mixture regardless of the choice of palladium catalyst, with the former isomer often being predominant. In contrast, extensive research has been conducted for the identification of efficient catalytic systems that can deliver arylated electron-rich olefins with high regioselectivity. The efforts of Hallberg, Cabri, and Xiao and many others have led to several methods for highly selective internal (α-) arylations of vinyl ethers, enamides, and various allylic compounds.[5−8] It has further been shown that palladium-catalyzed Heck reactions proceed via two different pathways, neutral or cationic: the cationic route using chelating bidentate ligands results in an electronically controlled insertion yielding α-arylation of electron-rich linear monosubstituted olefins, whereas neutral conditions instead promote β-arylation out of sterical reasons.[6] Recent density functional theory (DFT) calculations have provided further support to this rationale.[9,10]

In 1988, Andersson and Hallberg made the first attempts to develop a protocol for selective terminal arylation of electron-rich n-butyl vinyl ether by employing reactive aroyl chlorides

(1) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146−151.
(2) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411.
(3) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.
(4) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963.
(5) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433−1445.
(6) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.
(7) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1133−1178.
(8) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751−760.
(9) von Schenck, H.; Åkermark, B.;Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503−3508.
(10) Deeth, R. J.; Smith, A.; Brown, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7144−7151.

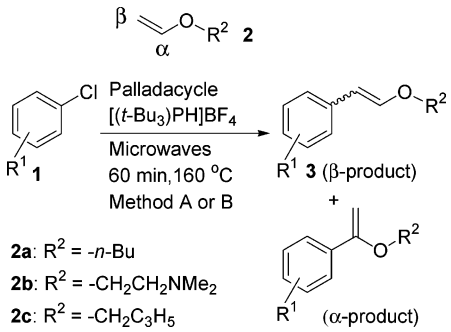
10.1021/jo0602367 CCC: $33.50
Published on Web 04/20/2006

as Ar−Pd precursor under decarbonylative reflux conditions.[11] Fair β-selectivities (up to $\beta/\alpha = 90:10$) and good yields (40−60%) were obtained with aryl moieties carrying electron-withdrawing aryl groups. The authors also concluded that the type of halide coordinating to the metal center in the oxidative addition intermediate had a profound influence on the regioselectivity, with chloride giving highest selectivity for the linear β-product.[12] Since the direct use of aryl chlorides species was not generally possible at this time, a series of alkyl vinyl ethers equipped with palladium-presenting amino groups was instead introduced, allowing highly selective β-arylations via a pseudo intramolecular insertion process.[13,14] However, for effective use in synthesis, the development of β-selective procedures for arylation of electron-rich standard olefins without metal-coordinating auxiliaries is desirable.

By addition of a novel tetraphosphine-palladium catalyst, Doucet and Santelli obtained high regioselectivities favoring the linear isomer using sterically demanding cyclohexyl or *tert*-butyl vinyl ether and electron-deficient aryl bromides.[15] With unhindered *n*-butyl vinyl ether only poor α/β ratios were obtained. In contrast, with a particular poly(ethylene glycol) polymer (PEG-2000), high terminal selectivities were recently reported with both aryl bromides carrying EWGs (electron-withdrawing groups) or EDGs (electron-donating groups) and simple palladium acetate.[16]

A substantial improvement in Heck methodology was the pioneering discovery by Fu that the electron-rich and bulky P(*t*-Bu)$_3$ ligand promotes smooth oxidative addition of aryl chlorides, thus enabling Heck reactions with this class of readily available starting materials.[17,18] Since the first reports, there has been a notable interest in further exploring this versatile ligand, and the corresponding air-stable preligand [(*t*-Bu$_3$)PH]BF$_4$, both from a mechanistic point of view[19−23] and from a preparative perspective.[24] Importantly, Fu investigated the effect of P(*t*-Bu)$_3$ with *n*-butyl vinyl ether in two isolated entries using *p*-(dimethylamino)bromobenzene and *p*-chloroacetophenone as substrates and Pd$_2$(dba)$_3$ as the palladium source.[17] Both arylations were performed under an inert atmosphere at ambient temperature in 1,4-dioxane for 33−48 h. The reaction with the electron-rich aryl bromide led to a β/α ratio of 20:80, whereas the activated chloride furnished a higher β/α-selectivity of 91:9 with 5% remaining *p*-chloroacetophenone. The products were isolated in high yields, 97% and 87%, respectively, although not as individual regioisomers but as mixtures. Based on the impressive outcome of the latter reaction, the unique properties of the P(*t*-Bu)$_3$ ligand and the high sensitivity of the Heck reaction to experimental parameters raised a number of important questions: (a) Can fine-tuning of a P(*t*-Bu)$_3$-based arylation system furnish a general β-selective Heck protocol for unfunctionalized alkyl vinyl ethers and aryl chlorides equipped with both electron-withdrawing and electron-donating substituents? (b) Is it possible to reduce the long reaction time and identify a more convenient non-inert procedure? (c) How can an improved regiochemical outcome be analyzed and understood?

SCHEME 1



We have now specifically addressed the transformation depicted in Scheme 1, following a combined experimental and computational approach. We herein report that palladium-catalyzed arylation of the less-substituted β-position of the vinyl ether double bond can be efficiently and rapidly performed under air using aryl chlorides, P(*t*-Bu)$_3$ liberating [(*t*-Bu$_3$)PH]BF$_4$, and high-density microwave processing, providing rapid and smooth in situ heating.[25,26] Enhanced β-selectivities are observed with [(*t*-Bu$_3$)PH]BF$_4$ compared to PPh$_3$ and with PEG-200,[27] carrying free hydroxyl terminals, compared to aqueous DMF. Complementary DFT calculations provide an explanation for the experimental regiochemical outcome with respect to the *para*-substituent of the aryl chloride and the properties of the phosphine ligand. In addition, the preparative usefulness of this arylation procedure is illustrated in the key step of a new synthetic route to Betaxolol, an approved well-known clinically used β-blocker.

Results

Experimental Results. We decided to initiate the investigation using a series of electronically and sterically different aryl chlorides (**1a**−**i**) with *n*-butyl vinyl ether (**2a**) as the model olefin and aqueous DMF as the solvent in microwave-transparent reaction vessels sealed under air. The first set of reactions demonstrated that Cy$_2$NMe was a useful base and that [(*t*-Bu$_3$)-PH]BF$_4$ served as a reliable source of P(*t*-Bu)$_3$ under non-inert microwave conditions. Among different alternatives of palladium(0) sources, Herrman's palladacycle[28] repeatedly delivered higher yields and better β-selectivities with sluggish *p*-anisyl chloride than other alternatives [Pd(OAc)$_2$, Pd(PCy$_3$)$_2$, and Pd$_2$(dba)$_3$]. Without [(*t*-Bu$_3$)PH]BF$_4$ no produc-

(11) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235−239.
(12) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 2112−2114.
(13) Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783−792.
(14) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217−8225.
(15) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2004**, 1561−1564.
(16) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399−4401.
(17) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.
(18) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.
(19) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752.
(20) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178−13179.
(21) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746−4748.
(22) Stambuli, J. P.; Incarvito, C. D.; Buehl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184−1194.
(23) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944−6945.
(24) Datta, G. K.; Vallin, K. S. A.; Larhed, M. *Mol. Div.* **2003**, *7*, 107−114.
(25) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.
(26) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.
(27) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195−218.
(28) Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23−41.

TABLE 1. Terminal β-Arylation of Alkyl Vinyl Ethers with Aryl Chlorides

entry	Ar-Cl	olefin	product	method	β/α	yield[a](%)
1	4-NO_2-Ph-Cl		4-NO_2-Ph–OBu	A	97:3	61
	1a	**2a**	**3a**	B	98:2	60
2	4-CF_3-Ph-Cl		4-CF_3-Ph–OBu	A	97:3	64
	1b	**2a**	**3b**	B	98:2	65
3	4-CHO-Ph-Cl		4-CHO-Ph–OBu	A	97:3	65
	1c	**2a**	**3c**	B	98:2	62
4	4-Ac-Ph-Cl		4-Ac-Ph–OBu	A	97:3	75
	1d	**2a**	**3d**	B	98:2	70
5	2-Cl-Naphthalene		2-Naphthyl–OBu	A	89:11	62
	1e	**2a**	**3e**	B	92:8	60
6	Ph-Cl		Ph–OBu	A	90:10	60
	1f	**2a**	**3f**	B	93:7	59
7	4-Me-Ph-Cl		4-Me-Ph–OBu	A	80:20	52
	1g	**2a**	**3g**	B	83:17	52
8	2-Me-Ph-Cl		2-Me-Ph–OBu	A	80:20	53
	1h	**2a**	**3h**	B	82:18	54
9	4-MeO-Ph-Cl		4-MeO-Ph–OBu	A	65:35	40
	1i	**2a**	**3i**	B	78:22	46
				A		<1[b]
				A		0[c]
				A	48:52	7[d]
				A	55:45	9[e]
				A	85:15	63
10	**1i**		4-MeO-Ph–O–$(CH_2)_2NMe_2$	B	90:10	70
		2b	**3j**			

Reaction conditions. **Method A**: 1.0 mmol of **1**, 3.0 mmol of **2**, 0.05 mmol of palladacycle, 0.10 mmol of [(*t*-Bu_3)PH]BF_4, 3.0 mmol of Cy_2NMe, 200 mL of H_2O, and 2 mL of DMF in sealed vessels. Microwave heating, 160 °C for 60 min. **Method B**: 1.0 mmol of **1**, 3.0 mmol of **2**, 0.05 mmol of palladacycle, 0.10 mmol of [(*t*-Bu_3)PH]BF_4, 5.0 mmol of PMP, and 2 mL of PEG-200 in sealed vessels. Microwave heating, 160 °C for 60 min. [a] Isolated yields of β-products, in all cases, >95% purity of **3** by GC−MS and ^{1}H NMR, average of five runs. β/α ratio, in all cases, was determined by response factors in GC−MS between the β-products and the α-product plus the corresponding aryl methyl ketone. [b] Palladacycle but no [(*t*-Bu_3)PH]BF_4. [c] 0.10 mmol of $Pd(OAc)_2$ instead of palladacycle. [d] 0.10 mmol of $Pd(PCy_3)_2$ instead of palladacycle. 70% conversion of **1i**. [e] 0.05 mmol of $Pd_2(dba)_3$ instead of palladacycle, 65% conversion of **1i**.

tive reaction occurred (Table 1, Method A, entry 9), proving that the active catalyst must be a Pd(0)−P(*t*-Bu)$_3$ species and not a Pd(0)−P(*o*-tol)$_3$ complex. Having identified an appropriate 1 mmol protocol employing 3 equiv of **2a**, 3 equiv Cy_2NMe, 5% palladacycle, and 10% [(*t*-Bu_3)PH]BF_4 (Method A), all available aryl chlorides were investigated (Table 1). Controlled microwave heating for 60 min at 160 °C gave, in all cases, more than 98% conversion of the limiting aryl chloride, whereas shorter reaction times resulted in incomplete conversions. Due to partial hydrolysis of the α-arylated vinyl ethers during the reaction, the β/α-regioselectivity was, in all cases, determined as the GC−MS ratio between the β-products and the α-product plus the corresponding aryl methyl ketone. The value of the GC−MS area for the aryl methyl ketone was checked by crude ^{1}H NMR and was always corrected by implementing an experimentally determined response factor (see Supporting Information). The somewhat disappointing isolated yields of **3a**−**i** may partly be explained by the small reaction scale and, with electron-rich **1g**−**i** (entries 7−9), by competing α-arylation. However, the most important reason was that linear **3** was very carefully purified to remove all traces of the α-arylated isomer. The selectivity for the formation of the linear β-product varied from 97:3 for aryl groups with EWGs (entries 1−4) to 65:35 for the *p*-methoxy-substituted **3i** (entry 9). To improve the latter selectivity with **3i**, an arylation was conducted with catalyst presenting **2b**[29] instead of **2a**, increasing the β/α-selectivity to 85/15 and the isolated yield to 63% (entry 10).

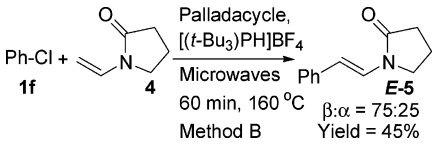
Compared to the room-temperature reaction reported by Fu, with *n*-butyl vinyl ether and **1d** using 1.5% $Pd_2(dba)_3$ and 3.0% P(*t*-Bu)$_3$,[17] our microwave procedure (Table 1, entry 4) provides slightly better regiocontrol and comparable yield [β/α = 97:3 vs 91:9 and 75% (β-product only) vs 87% (β + α and 5% unreacted **1d**)]. To compare with Fu's reported reaction between *p*-(dimethylamino)bromobenzene and *n*-butyl vinyl ether, we also investigated our methodology (Method A, not presented in Table 1) using the same aryl bromide substrate. Interestingly, we obtained an improved regiochemical outcome (β/α = 34:66 vs 20:80), although the isolated yields of the β,α mixtures were different (80% vs 97%). The lower yield in our case can be explained by dehalogenetion of the aryl bromide at the high reaction temperature (160 °C). Classic oil bath heating at 160 °C for 1 or 2 h of the reaction depicted in entry 9 (Table 1) did not consume all aryl chloride, a result that might be explained by the lack of wall effects (and subsequent catalyst decomposition) applying microwave heating.[25,30]

Inspired by the high linear selectivity reported by Chandrasekhar for Heck arylations of *n*-butyl vinyl ether with aryl bromides in environmentally friendly PEG-2000,[16] we decided to explore different PEG alternatives[27] as solvents also with the palladacycle/[(*t*-Bu_3)PH]BF_4 catalytic system. Unfortunately, we were not able to repeat Chandrasekhar's high regiochemical outcome using aryl bromides under the published conditions. With phenyl chloride (**1f**) we screened four different types of PEG polymers according to Method A, except for the choices of solvent and sterically hindered base [pentamethyl piperidin (PMP) instead of Cy_2NMe]. Exploring PEG-200 and PEG-2000 alternatives with methylated chain-end hydroxyl groups (masked) or PEG 2000 with free hydroxyl functions (unmasked), only incomplete reactions with β/α ratios of up to 85:15 were obtained, nor did PEG monomer-like DME or ethylene glycol furnish more than 50% conversion. On the other hand, the use of unmasked PEG-200 provided useful arylations (Method B, Table 1). The solvent switch from aqueous DMF to non-methylated PEG-200 resulted in comparable regioselectivity in almost all cases except for electron-rich aryl chlorides, for which slightly improved β-selectivities were obtained (Table 1, entries 7−9). Importantly, the PEG-200 polymer was stable at the high reaction temperature of 160 °C and also supported the chelation-controlled vinylation in the last entry of Table 1, providing 70% of product **3j**. In a final sequence of vinyl ether experiments, the coupling between *E*/*Z*-ethyl 1-propenyl ether and 2-naphthyl chloride (**1e**) was examined in order to evaluate the effect of a methyl substituent on the vinyl ether β-carbon. All attempted reactions were sluggish, but the β/α ratios were consistently close to 60:40, indicating a small preference for terminal arylation also when an unfavorable steric factor was present.

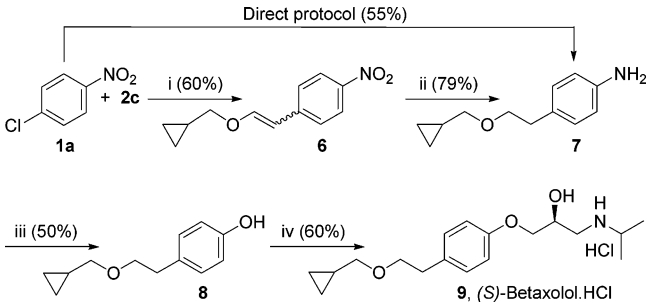
Considering the fact that enamides are electron-rich olefins with a reactivity profile similar to vinyl ethers, we decided to

(29) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757−5761.
(30) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665−1692.

SCHEME 2



SCHEME 3

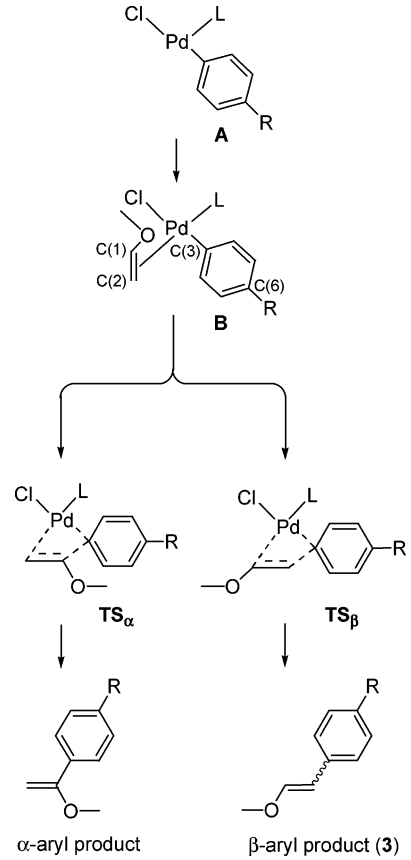


i. Method A
ii. Pd/C, $HCOONH_4$, EtOH, 80 °C, 40 min, Microwaves
iii. $NaNO_2/H_2SO_4$; 0-5 °C, H_2O
iv. a. (*R*)-3-Isopropylamino-1,2-epoxypropane; NaOH; Reflux; 8 h
b. Dry HCl gas in Et_2O medium

investigate if vinyl pyrrolidinone **4** might be prone to undergo selective β-arylation using either Method A or B. Unfortunately, neither method delivered product **5** with high regioselectivity although the best results were obtained with Method B (Scheme 2). The moderate yield and selectivity illustrate the remaining problem to discover a fully general method for β-arylation of all types of electron-rich olefins. To our best knowledge, this is the first example of a terminal arylation of an enamide using an aryl chloride as coupling partner.[18]

The terminal Heck arylation of alkyl vinyl ethers has high synthetic potential.[31] Thus, we wanted to apply our selective microwave procedure to a synthetic target. The racemic form of Betaxolol is used for the treatment of hypertension and angina pectoris. Several approaches for the synthesis of this molecule have been reported, but no methods have so far started from easily available and inexpensive **1a**.[32,33] Cyclopropylmethyl vinyl ether **2c** was first easily prepared by a palladium-catalyzed transvinylation from cyclopropylmethanol and ethyl vinyl ether using 2,2′-bipyridyl as the ligand. Next, and slightly surprisingly, the critical Heck arylation was found to give the best outcome in aqueous DMF (Method A instead of B), affording a 60% isolated yield of key intermediate **6** in a highly regioselective coupling (β/α = 97:3, Scheme 3). Subsequent Pd/C-catalyzed transfer hydrogenation using ammonium formiate as the hydride source and microwaves as the energy source reduced both the double bond and the nitro group simultaneously and allowed isolation of **7** in 79% yield. Alternatively, aryl chloride **1a** was directly converted to *para*-substituted aniline **7**, without purifying **6**, in a slightly improved one-step yield. Diazotization with sodium nitrite and a productive reaction with water was then achieved, although the small scale (0.5 mmol) prohibited a yield better than 50% of phenol **8**. Addition of (*R*)-3-isopropylamino-1,2-epoxypropane[34] and reflux in ethanol for 8 h gave the active (*S*)-enantiomer of Betaxolol as the free base. The corresponding

SCHEME 4. Regio-Determining Insertion of Methyl Vinyl Ether



hydrochloride salt was obtained in high purity after treatment with dry HCl (gas) in diethyl ether and following crystallization. Altogether, (*S*)-Betaxolol·HCl was prepared in 60% yield based on **8** and in 16.5% overall yield from **1a** (Scheme 3).

Computational Results. DFT calculations at the B3LYP level of theory were performed for the regioselectivity-determining insertion step in the Heck reaction, following a neutral pathway. A set of *para*-substituted [C(6)] phenylpalladium(II) complexes were investigated (Scheme 4). Results of the calculations and the experiments were subsequently compared with respect to regioselectivity. Computational details are presented in Supporting Information. The electronic influence of the phenyl *para*-substituent on the regiochemical outcome was investigated by varying the substituent R (R = $-OCH_3$, $-C_{10}H_7$, -H, -CHO, $-NO_2$), including electron-donating as well as electron-withdrawing groups (see also Table 1). Steric influences of palladium-coordinating phosphines were probed by ligands (L) of increasing size (L = PH_3, PPh_3, P(*t*-Bu)$_3$). The inserting *n*-butyl vinyl ether that was used in experiments was modeled by methyl vinyl ether in the calculations.

In the Heck arylation sequence, the first catalytic step is the oxidative addition of Pd(0) to an aryl halide, affording σ-complex **A**. The resting state prior to insertion is the π-complex, **B**, where the olefin is coordinated with the carbon−carbon double bond perpendicular to the plane defined by the square planar geometry of the 16e$^-$ complex (Scheme 4, Figure 1). Following the π-coordination, the olefin rotates clockwise or counterclockwise into the ligand plane, forming the transition state

(31) Hallberg, A.; Westfelt, L.; Andersson, C. M. *Synth. Commun.* **1985**, *15*, 1131−1136.
(32) Manoury, P. M.; Binet, J. L.; Rousseau, J.; Lefevre-Borg, F. M.; Cavero, I. G. *J. Med. Chem.* **1987**, *30*, 1003−1011.
(33) Di Bono, G.; Scilimati, A. *Synthesis* **1995**, 699−702.
(34) Kan, K.; Miyama, A.; Hamaguchi, S.; Ohashi, T.; Watanabe, K. *Agric. Biol. Chem.* **1985**, *49*, 1669−1674.

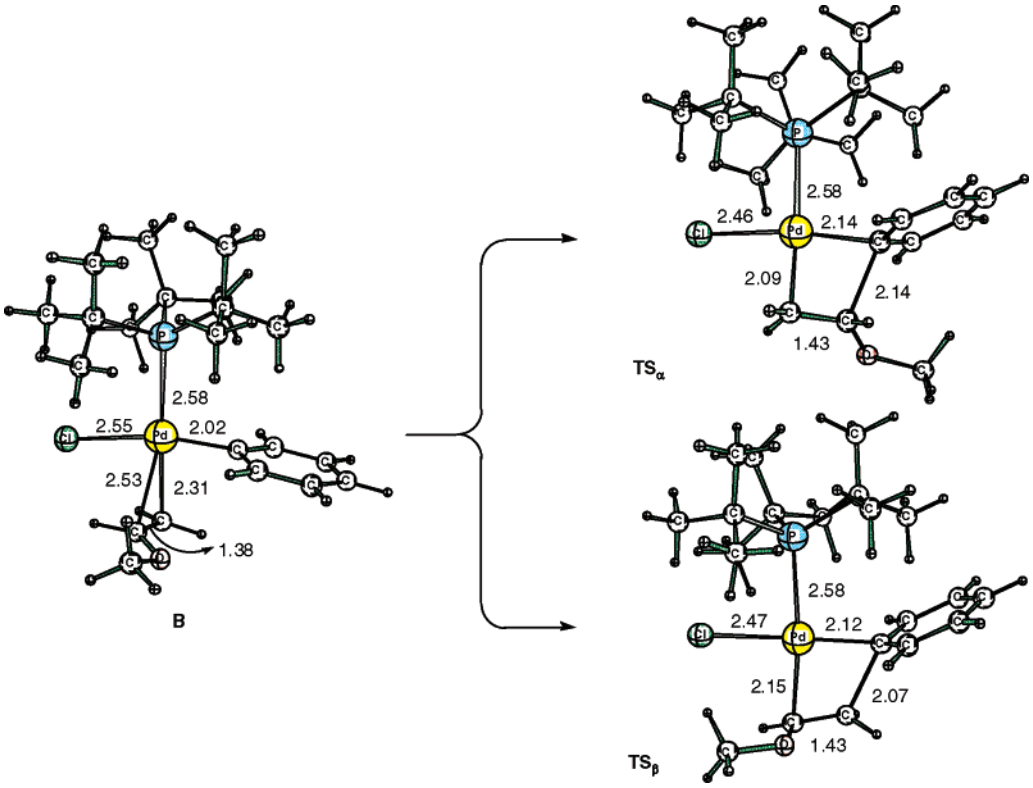


FIGURE 1. Representative structures of π-coordinated olefin species and the two possible transition state structures **TS**$_\alpha$ and **TS**$_\beta$.

geometries **TS**$_\alpha$ or **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 the TS and the π-complex energies. Subsequent β-hydride elimination releases the branched (α-) or linear (β-) products. Tables 2−4 summarize the computational results.

Discussion

Experimentally Found Ligand and Solvent Effects. To investigate the effect of different ligands and solvents, two series of reactions were performed. In the first series P(*t*-Bu)$_3$ was compared with traditional PPh_3 (Table 5). The arylations were conducted in aqueous DMF starting from activated **1a**, **1c**, and *p*-bromobenzaldehyde (**1z**) and provided full conversions after 60 min at 160 °C. Interestingly, the alkyl phosphine ligand produced a higher selectivity toward the linear product with all three aryl halides, illustrating the regio-determining power of P(*t*-Bu)$_3$. No difference in product pattern was observed using **1c** or the directly comparable aryl bromide **1z**. Not only were the obtained regioselectivities higher with [(*t*-Bu$_3$)PH]BF$_4$, but the isolated yields of **3** were also higher compared to the corresponding PPh_3-promoted reactions (Table 5). Reactions with only Herrmann's catalyst produced almost identical results as the PPh_3-palladacycle combination.

In the second reaction sequence, the effects of phosphine ligands in DMF/water (Method A type conditions) and PEG-200 (Method B type conditions) were studied (Table 6). *p*-Tolyl bromide was used as the arylating agent to secure complete conversion of an electron-rich aryl moiety also in the absence of [(*t*-Bu$_3$)PH]BF$_4$. Please note that reactions without PPh_3 or [(*t*-Bu$_3$)PH]BF$_4$ were not completely phosphine-free since Herrman's palladacycle was used as the palladium source in all cases. Regardless of the solvent, (*t*-Bu$_3$)P-controlled arylations furnished β-selectivities higher than those of the PPh_3-mediated counterparts. One surprising finding regarding the isomeric distribution was that the use of unmasked PEG-200, without the addition of an extra ligand, delivered higher β-selectivity than the reaction in the presence of P(*t*-Bu)$_3$ (84:16 vs 74:26, entries 6 and 5 in Table 6), indicating a direct involvement of the PEG-solvent in the insertion process.

TABLE 2. Computational Results of the Migratory Insertion of Methyl Vinyl Ether with Selected *para*-Substituted Neutral Arylpalladium(II) Complexes

entry	R	ligand (L)	ΔE_π[a]	ΔE^*_α[b]	ΔE^*_β[c]	$\Delta\Delta E^*$[d]	$\Delta E_{Pd\text{-}Cl}$[e]	Acc. MO[f]
1	-OMe	PH_3	-20.4	17.5	17.8	-0.3	-122.5	-0.87
2		PH_3	-22.3	19.4	18.7	0.7	-125.8	-1.58
3	-H	PH_3	-21.3	19.4	18.3	1.1	-125.9	-0.89
4	-CHO	PH_3	-23.5	22.0	19.4	2.6	-132.1	-2.22
5	-NO_2	PH_3	-23.9	23.4	20.6	2.8	-135.1	-3.10
6	-OMe	PPh_3	-15.0	19.8	20.3	-0.5	-114.0	-1.39
7	-H	PPh_3	-16.7	23.5	21.2	2.3	-115.5	-1.39
8	-CHO	PPh_3	-17.3	24.4	21.2	3.2	-121.5	-1.92
9	-OMe	P(*t*-Bu)$_3$	-9.6	20.9	20.2	0.7	-113.0	-0.57
10	-H	P(*t*-Bu)$_3$	-10.4	22.8	21.1	1.7	-114.0	-0.55
11	-CHO	P(*t*-Bu)$_3$	-10.9	25.1	21.3	3.8	-118.0	-2.03

[a] π-Complexation energy [kcal/mol]. [b] Reaction barrier of insertion forming the α-aryl product [kcal/mol]. [c] Reaction barrier of insertion forming the β-aryl product [kcal/mol]. [d] $\Delta\Delta E^* = \Delta E_\alpha^* - \Delta E_\beta^*$ [kcal/mol]. Pd−Cl coordination energy [kcal/mol]. [f] Energy of the accepting MO of **A** (the LUMO + 1) [eV].

TABLE 3. Selected Geometrical Parameters

entry	R	ligand (L)	$d_{Pd\text{-}C(1)}$[a]	$d_{Pd\text{-}C(2)}$[b]	ϕ [°][c]	θ [°][d]	φ_α [°][e]
1	-OMe	PH_3	2.44	2.27	92.9	169.5	4.6
2		PH_3	2.45	2.27	92.3	170.7	4.7
3	-H	PH_3	2.46	2.27	93.6	169.1	5.1
4	-CHO	PH_3	2.46	2.27	94.6	170.6	3.1
5	$-NO_2$	PH_3	2.47	2.27	93.9	171.0	2.3
6	-OMe	PPh_3	2.48	2.29	92.5	167.6	1.0
7	-H	PPh_3	2.49	2.30	92.6	167.1	9.8
8	-CHO	PPh_3	2.46	2.28	92.8	168.4	7.5
9	-OMe	P(*t*-Bu)$_3$	2.52	2.31	97.7	164.0	11.8
10	-H	P(*t*-Bu)$_3$	2.53	2.31	99.6	161.5	10.4
11	-CHO	P(*t*-Bu)$_3$	2.54	2.31	97.6	164.9	9.8

[a] Pd−C(1) bond length of **B** [Å]. [b] Pd−C(2) bond length of **B** [Å]. [c] Angle P−Pd−C(3) in **A**. [d] Angle Pd−C(3)−C(6) in **A**. [e] Dihedral angle C(3)−Pd-C(1)−C(2) for $\mathbf{TS}_\alpha$. [f] Dihedral angle C(3)−Pd-C(1)−C(2) for $\mathbf{TS}_\beta$.

TABLE 4. Coordination Strength of Ligands to Neutral Phenylpalladium(II) Complex B

entry	R	ligand (L)	ΔE_L[a]
1	-H	PPh_3	−26.7
2	-H	P(*t*-Bu)$_3$	−19.0
3	-H	P(*o*-tol)$_3$	−22.6
4	-H	PEG ($CH_3OC_2H_4OCH_3$)	−16.7
5	-H	DMF	−17.8
6	-H	PMP	−7.4
7	-H	Cy_2NMe	−14.0

[a] Coordination energy of various potential ligands to **B** [kcal/mol].

TABLE 5. Regiochemical Outcome of Arylations with *n*-Butyl Vinyl Ether and [(*t*-Bu$_3$)PH]BF$_4$ or PPh_3 in Aqueous DMF[a]

entry	Ar-X	phosphine ligand (L)	β/α	isolated yield of **3**
1	**1a**	PPh_3	84:16	26
2	**1a**	[(*t*-Bu$_3$)PH]BF$_4$	96:4	61
3	**1c**	PPh_3	82:18	25
4	**1c**	[(*t*-Bu$_3$)PH]BF$_4$	96:4	65
5	**1z**	PPh_3	80:20	21
6	**1z**	[(*t*-Bu$_3$)PH]BF$_4$	98:2	66

[a] Reaction conditions: 1.0 mmol of aryl halide**,** 3.0 mmol of **2a**, 0.05 mmol of palladacycle, 0.10 mmol of ligand or preligand, 3.0 mmol of Cy_2NMe, 200 mL of H_2O, and 2 mL of DMF in sealed vessels. Microwave heating, 160 °C for 60 min delivered >95% conversion. Isolated yields, >95% purity of linear β-product **3** by GC−MS and ^{1}H NMR.

π-Complexation. The π-complex forms through a donation-backdonation interaction between the enol double bond and the metal center, with the typical geometry exemplified by structure **B** in Figure 1. From the computational results in Table 2 it can be observed that EDGs produce the weakest π-interaction, with the interaction becoming stronger as R becomes more electron-withdrawing. This is a general trend for each group of L (PH_3, PPh_3, P(*t*-Bu)$_3$). A good correlation between the stability of the accepting molecular orbital of **A** and ΔE_π is observed (Table 2). The influence of this electronic component is diminished as the size of the coordinating phosphine increases, in effect displacing the olefin further away from the metal center (see distance parameters $d_{Pd-C(1)}$ and $d_{Pd-C(2)}$ in Table 3).

TABLE 6. Impact of Solvents and Ligands in the Reaction between *p*-Tolyl Bromide and Alkyl Vinyl Ether[a]

entry	solvent	phosphine ligand (L)	β/α
1	DMF/water	PPh_3	62:38
2	DMF/water	[(*t*-Bu$_3$)PH]BF$_4$	70:30
3	DMF/water	None	64:36
4	PEG-200	PPh_3	60:40
5	PEG-200	[(*t*-Bu$_3$)PH]BF$_4$	74:26
6	PEG-200	None	84:16

[a] Reaction conditions: 1.0 mmol of *p*-tolyl bromide, 3.0 mmol of **2a**, 0.05 mmol of palladacycle, 0.10 mmol of ligand or no ligand, 3.0 mmol of PMP, 200 mL of H_2O, and 2 mL of DMF or 2 mL of unmasked PEG-200 in sealed vessels. Microwave heating, 160 °C for 60 min delivered >95% conversion.

Insertion Barrier. In related theoretical studies of the Heck reaction, using sterically undemanding ligand systems coordinating to Pd(II), it has been observed that high insertion barriers correlate with large values of ΔE_π. This has been rationalized by the fact that a considerable part of the π-coordination is lost as the TS structure is formed.[35] In the present work, this general rule still holds true within each investigated subset (L = PH_3, PPh_3, P(*t*-Bu)$_3$). However, although the increased size of L leads to a corresponding decrease of ΔE_π (compare entries 1, 6, 9 or 3, 7, 10 or 4, 8, 11 in Table 2), the insertion barriers still remain high and even increase. From this it can be concluded that destabilization of π-complex **B** due to the size of L is accompanied by a general destabilization of TS_α and TS_β. The geometrical parameters given in Table 3 lend support to this notion. As the size of the phosphine increases, the phenyl ring is both deflected and tilted away from L, as can be seen from the angles ϕ and θ, respectively. Comparing entries 1, 6, 9 or 3, 7, 10 or 4, 8, 11 in Table 3, it is seen that ϕ and θ change notably only when L = P(*t*-Bu)$_3$. This displacement of the metal-bonding phenyl ring restricts the available space for transition state formation (i.e., when the olefin rotates into the ligand plane), in effect destabilizing the TS structure (see Figure 1). An increase of the dihedral angle φ_α with increasing size of L illustrates the more congested TS geometry in a direct way (Table 3).

Regioselectivity. Both electronic and steric effects influence the regiochemical outcome of the studied reaction. For each type of ligand (PH_3, PPh_3, P(*t*-Bu)$_3$), the terminal selectivity rises with the increasing electron-withdrawing character of the C(6)-substituent (R) in the aryl ring (Table 2, computational numbering). This trend can be set in the context of the regiochemistry of Heck couplings under neutral and cationic conditions.[6,7,9,10] It has been observed both in experimental and theoretical work that neutral reaction conditions favor terminal β-selectivity for electron-rich olefins.[7,9,36] Cationic conditions, on the other hand, lead to increasingly α-selective insertions for the same olefin. In Table 2, the coordination strength (ΔE_{Pd-Cl}) of chloride to the remaining cationic fragment of **B** is listed as a function of the phenyl *para*-substituent (R). In agreement with the above reasoning we note that more neutral conditions, with electron-withdrawing substituents producing relatively strong Cl−Pd coordinations, correlate with a preference for β-selectivity. Conversely, electron-donating groups producing weaker Cl−Pd coordinations favor the formation of

(35) von Schenck, H.; Strömberg, S.; Zetterberg, K.; Ludwig, M.; Åkermark, B.; Svensson, M. *Organometallics* **2001**, *20*, 2813−2819.

(36) Deeth, R. J.; Smith, A.; Hii, K. K.; Brown, J. M. *Tetrahedron Lett.* **1998**, *39*, 3229−3232.

branched α-products (compare entries 1−5 for L = PH_3, entries 6−8 for L = PPh_3, entries 9−11 for L = P(*t*-Bu)$_3$). These results match the preparative results presented in Table 1.

The influence of steric bulk has already been mentioned in a general context in the previous section, where it was noted that bulky phosphines restrict the available space for transition state formation, thereby destabilizing the transition state structures. It is reasonable to expect $\mathbf{TS}_\alpha$ to be more destabilized than $\mathbf{TS}_\beta$ as a result of steric interaction between the olefin methoxy group and phenyl ring, and hence we anticipate an increase in *β*-selectivity as L increases in size. This can be directly observed from the values of $\Delta\Delta E^*$, given in Table 2. The more bulky L = P(*t*-Bu)$_3$ gives improved *β*-selectivity compared to L = PPh_3, a fact that is verified by experimental results (Tables 5 and 6).

Ligand Coordination. The coordination strengths of potential ligands L in structure **B** are listed in Table 4, where L represents phosphines as well as solvent molecules and amine bases available in the reaction mixtures. Since the electronic and steric character of L will influence the regiochemical outcome, an evaluation of the relative stabilities of the resting states is important (Table 4). Two standard conditions have been used with DMF and non-methylated PEG-200 as solvents, with two different tertiary amines as bases and P(*t*-Bu)$_3$ as the ligand (Method A and B, Table 1). The coordination energy of P(*o*-tol)$_3$ was also calculated since Herrman's palladacycle is prepared from this phosphine. Results from Table 4 verify the expected result that all three phosphines coordinate more strongly to Pd than either of the solvents or bases. It should be noted that theory predicts stronger coordination of PPh_3 compared to that of P(*t*-Bu)$_3$, ΔE_L = 26.7 and 19.0 kcal/mol, respectively. As explained above, the bulkier P(*t*-Bu)$_3$ improves *β*-selectivity compared to PPh_3.

Effects of Unmasked PEG-200. The present experimental work shows that unmasked PEG-200 can have a notable effect on the regioselectivity of the insertion (Method B, Table 1 and Table 6). For the equivalent reactants and reaction conditions, a mixture of PPh_3/PEG-200 gives a similar regiochemical outcome as PPh_3/DMF, 60:40 and 62:38, respectively (entry 1 and 4, Table 6). A mixture of P(*t*-Bu)$_3$/PEG-200 provides a slightly improved *β*/α ratio compared to that of P(*t*-Bu)$_3$/DMF, 74:26 and 70:30, respectively (entry 2 and 5). Using PEG-200 without phosphine ligands improves *β*-selectivity even further, to 84:16. These observations can be related to the values of ΔE_L in Table 4 (PEG is modeled by $CH_3OC_2H_4OCH_3$). ΔE_L = 26.7 kcal/mol for PPh_3 and 16.7 kcal/mol for PEG, leading to the conclusion that the phosphine will be coordinated to the metal center whether PEG is present or not, leaving the regiochemistry unaffected. For P(*t*-Bu)$_3$ ΔE_L = 19.0 kcal/mol, therefore coordinating somewhat stronger than PEG to Pd(II). Considering the relatively high concentration of PEG compared to that of P(*t*-Bu)$_3$, it is possible that resting state structure **B** will be present in the reaction mixture where PEG is coordinating to the metal center, resulting in a net increase in *β*-selectivity. The fact that the reaction proceeds in non-methylated PEG-200 in the absence of phosphine and with improved *β*-selectivity supports the idea that PEG-200 affects the reaction mechanism through a direct interaction between the polymer and the catalyst. An exhaustive study of the mechanism of PEG influence on reaction regioselectivity is very demanding, both from an experimental and computational point of view, and is not within the scope of the present work. However, a possible explanation can be put forth on the basis of the stabilization of

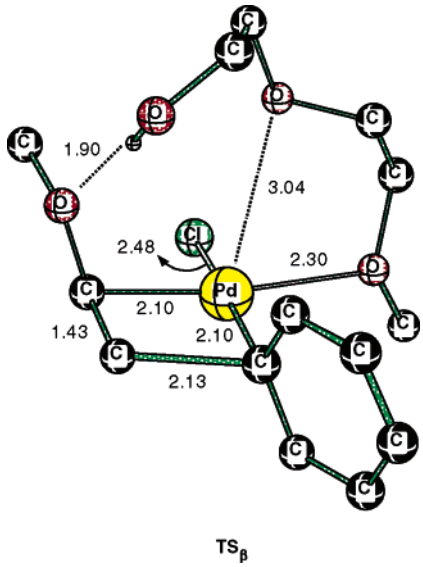


FIGURE 2. Optimized structure of $\mathbf{TS}_\beta$ stabilized by hydrogen bond interaction between insertion olefin and PEG chain-end hydroxyl. Only the polar hydrogen is displayed, for clarity.

$\mathbf{TS}_\beta$ in the presence of unmasked PEG-200. A transition state structure was found where the chain-end hydroxyl group of a PEG model stabilized $\mathbf{TS}_\beta$ through hydrogen bonding to the ether oxygen of the inserting olefin (see Figure 2). The stabilizing effect of the hydrogen bond was found to be 3.8 kcal/mol, a noteworthy influence.

The fact that the chain-end hydroxyls are involved in the reaction mechanism is supported by experimental results using Method B type conditions, phenyl chloride (**1f**), and *n*-butyl vinyl ether (**2a**). Masked PEG-200, with methoxy terminals, only gives partial conversion of **1f** and does not favor *β*-arylation to the same extent as the unmasked reference PEG-200 (*β*/α = 78:22 vs 93:7). The longer PEG chains with reduced net hydroxyl concentration or methylated hydroxy terminals also produced less *β*-product (*β*/α = 85:15) with only 5% conversion.

Conclusion

We have developed a general protocol for selective terminal Heck arylations of unfunctionalized alkyl vinyl ethers by using the P(*t*-Bu)$_3$-releasing salt [(*t*-Bu)$_3$PH]BF_4 as the essential additive. Furthermore, non-methylated PEG-200 was used as an environmentally friendly solvent and the rate of the reaction was increased by microwave heating. The bulky P(*t*-Bu)$_3$ ligand both enhanced the activity of the palladium catalyst, allowing utilization of sluggish aryl chlorides, and improved the terminal selectivity. DFT studies provided a rational insight into the origin of regiocontrol influenced by the bulky *tert*-butyl substituents of the phosphine ligand and subsequent steric interactions between the alkoxy group and the aromatic group, as well as the electronic properties of the aryl chloride. Hydrogen bonding of chain-end hydroxyl groups of PEG-200 to the vinyl ether oxygen was suggested to improve the regiochemical outcome. Finally, the value of the *β*-selective Heck procedure was illustrated in a novel synthesis of the *β*-adrenergic blocking agent Betaxolol.

Experimental Section

General Procedure for Terminal Arylation of Electron-Rich Olefins (Vinyl Ethers 2a and 2b) with Aryl Chlorides in DMF/

Water (Method A). A thick-wall glass vial (2−5 mL) with a Teflon-coated stirring bar was charged with aryl chloride (**1a**−**i**) (1.00 mmol), butyl vinyl ether (**2a**) (300.0 mg, 388 μL, 3.00 mmol) or (2-ethenyloxyethyl)dimethylamine (**2b**) (345.0 mg, 493 μL, 3.00 mmol), Herrmann's palladacycle (*trans*-di-(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)) (47.0 mg, 5.00 mol %), [(*t*-Bu)$_3$PH]BF$_4$ (29.0 mg, 10.00 mol %), and Cy$_2$NMe (645 μL, 3.00 mmol). DMF/H$_2$O (2 mL/200 μL) was thereafter added, followed by sealing of the vial under air. The vial was then heated to 160 °C by microwave irradiation for 60 min (ramp time approximately 40 s, hold time 3560 s). After cooling, the reaction mixture was filtered through a prepacked silica column having glass wool and a Celite bed on the top, and the filtrate was concentrated in vacuo. The residue was taken in CH_2Cl_2 and partitioned between saturated $NaHCO_3$ solution and water, respectively. Finally after separation, the organic phase was dried over K_2CO_3 and then evaporated to dryness. Chromatography of the crude product using radial thin-layer chromatography furnished pure **3a**−**i** and **3j** in good to moderate yield. All isolated products were >95% pure according to GC−MS.

General Procedure for Terminal Arylation of Electron-Rich Olefins (Vinyl Ethers 2a, 2b and Enamide 4) with Aryl Chlorides in PEG (Method B). A thick-wall glass vial (2−5 mL) with a Teflon-coated stirring bar was charged with aryl chloride (**1a**−**i**) (1.00 mmol), butyl vinyl ether (**2a**) (300 mg, 388 μL, 3.00 mmol) or (2-ethenyloxyethyl)dimethylamine (**2b**) (345.0 mg, 493 μL, 3.00 mmol) or 1-vinyl-2-pyrrolidinone (**4**) (333.0 mg, 319 μL, 3.00 mmol), Herrmann's palladacycle (*trans*-di-(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)) (47.0 mg, 5.00 mol %), [(*t*-Bu)$_3$PH]BF$_4$ (29.0 mg, 10.00 mol %), and PMP (904 μL, 5.00 mmol). PEG-200 (with free hydroxyl groups) (2 mL) was thereafter added, followed by sealing of the vial under air. The vial was then heated to 160 °C by microwave irradiation for 60 min (ramp time approximately 38 s, hold time 3562 s). After cooling, the reaction mixture was filtered through a prepacked silica column having glass wool and a Celite bed on the top, and the filtrate was concentrated in vacuo. The residue was taken in CH_2Cl_2 and partitioned between saturated $NaHCO_3$ solution and water, respectively. Finally after separation, the organic phase was dried over K_2CO_3 and then evaporated to dryness. Chromatography of this crude product using radial thin-layer chromatography furnished compounds **3a**−**i**, **3j**, and **5** in good to moderate yield. All isolated products were >95% pure according to GC−MS.

Synthesis of (*E*)-/(*Z*)-1-(2-Cyclopropylmethoxyethenyl)-4-nitrobenzene (6). A thick-wall glass vial (2−5 mL) with a Teflon-coated stirring bar was charged with 4-chloro nitrobenzene (**1a**) (157.0 mg, 1.00 mmol), cyclopropylmethyl vinyl ether (**2c**) (196.0 mg, 2.00 mmol), Herrmann's palladacycle (47.0 mg, 5.00 mol %), [(*t*-Bu)$_3$PH]BF$_4$ (29.0 mg, 10.00 mol %), and Cy$_2$NMe (645 μL, 3.00 mmol). DMF/H$_2$O (2 mL/200 μL) was thereafter added, followed by rapid sealing of the vial under air. The vial was then heated to 160 °C by microwave irradiation for 60 min (ramp time approximately 40 s, hold time 3560 s). After cooling, the reaction mixture was filtered through a prepacked silica column having glass wool and a Celite bed on the top, and the filtrate was concentrated in vacuo. The crude reaction mixture was taken in CH_2Cl_2 and partitioned between saturated $NaHCO_3$ solution and water, respectively. Finally, the organic phase was dried over K_2CO_3 and then evaporated to dryness. Chromatography of the crude product was performed using radial thin-layer chromatography. The isolated yield of **6** was 60% (132.0 mg) and the product was obtained as an *E*/*Z* mixture (7:2) in the form of a yellow sticky liquid (R_f (TLC) = 0.32 (ethyl acetate/isohexane = 5/95)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.31−0.35 (m, 2H) 0.62−0.67 (m, 2H) 1.18−1.25 (m, 1H) 3.74 (d, J = 7.4 Hz, 1.6H, *E*) 3.85 (d, J = 7.0 Hz, 0.4H, *Z*) 5.29 (d, J = 7.0 Hz, 0.2H, *Z*) 5.86 (d, J = 13.2 Hz, 0.8H, *E*) 6.45 (d, J = 7.0 Hz, 0.2H, *Z*) 7.21 (d, J = 13.2 Hz, 0.8H, *E*) 7.30−8.15 (m, 4H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.1, 3.2, 10.2, 10.8, 75.5, 78.8, 103.8, 104.6, 123.6, 124.2, 124.9, 128.3, 143.1, 143.9, 145.3, 150.5, 151.6. EI-MS *m*/*z* (relative intensity, 70 eV): 219 (M^+, 20), 165 (7), 148 (7.5), 118 (5), 89 (22), 55 (100). Elemental analysis: calcd C 65.74, H 5.98, N 6.39; found C 65.74, H 6.05, N 6.49.

Acknowledgment. We acknowledge financial support from the Swedish Research Council and the Knut and Alice Wallenberg's Foundation. We also thank Biotage AB for providing us with the microwave synthesizer. Parallelldatorcentrum (PDC) at the Swedish Royal Institute of Technology is acknowledged for providing computer facilities. Finally, we thank Dr. Xiongyu Wu, Dr. Peter Nilsson, Dr. Kristofer Olofsson, and Mr. Shane Peterson for intellectual contributions and Mr. Michael Lund Nielsen for technical support to this project.

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

JO0602367