Highly Regioselective, Sequential, and Multiple Palladium-Catalyzed Arylations of Vinyl Ethers Carrying a Coordinating Auxiliary: An Example of a Heck Triarylation Process

Peter Nilsson, Mats Larhed, and Anders Hallberg*

Contribution from the Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

Received April 23, 2001

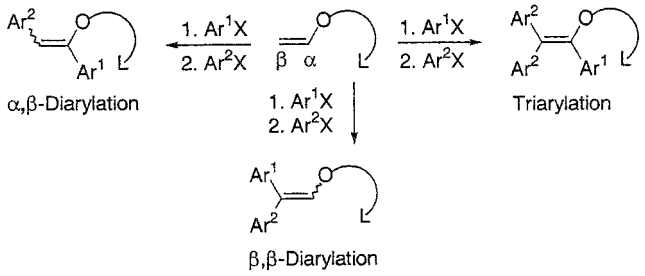
Abstract: This article describes the development of new auxiliary-accelerated Heck multiarylations by intramolecular presentation of the oxidative addition complex. The introduction of a specific, palladium-coordinating dimethylamino group allows for the desired chelation-accelerated and chelation-controlled tri- and diarylation reactions. We report (a) the first example of a Heck triarylation process, (b) highly selective palladium-catalyzed diarylations of alkyl vinyl ethers, and (c) a very rapid two-phase protocol for the microwave-assisted hydrolysis of amino-substituted, arylated vinyl ethers constituting an entry to diarylated ethanals and substituted desoxybenzoins. X-ray structures and product patterns support the suggested substrate-controlled Heck reaction pathway. The catalyst-directing alkyl dimethylamino functionality was rapidly (1−2 min) and efficiently released by microwave hydrolysis after Heck multiarylation reactions. The liberated aromatic carbonyl compounds were thereafter isolated and fully characterized.

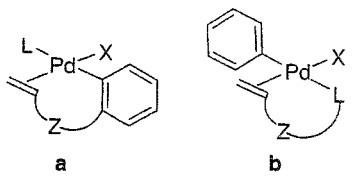
Introduction

The palladium-catalyzed vinylic substitution reaction (the Heck reaction) enjoys considerable popularity as a reliable and general method for carbon−carbon bond formation.[1] Although the traditional intermolecular Heck arylation has found wide utility, the reaction is essentially limited to the monoarylations of olefins, the success of which is largely dependent on which type of olefin is used, and on the sensitivity of the reaction to steric and electronic factors.[1] An extension of the Heck methodology to include selective di- and triarylations appears attractive and should increase the preparative scope considerably.[2]

The intramolecular version of the Heck arylation perhaps constitutes the most important development of the Heck arylation reaction in recent times.[3] The ability of intramolecular factors to overcome the reluctance of substituted alkenes to participate in the Heck insertion process allows the assembly of complex and sterically congested molecules. These synthetically valuable reactions rely upon the ready formation of a transient intramolecular π-complex (**a**). We,[4] and others,[5] have reported previously on the utilization of chelation to control the regioselectivity[6] of intermolecular vinyl ether arylations. The observed increase in reaction rate using substrates with a coordinating, metal-directing auxiliary[7] suggested that intermediate π-complexes of the type (**b**) might also facilitate sterically unfavorable intermolecular vinylic polysubstitutions. We have now specifically addressed the transformations depicted in Scheme 1 following such a strategy. Importantly, new catalytic systems have made it possible for excellent control of regioselectivity in Heck couplings with functionalized electron-rich olefins,[1c,4,5a,8] a requirement for success.

Scheme 1





We report multiple and selective vinylic substitution reactions involving nonsubstituted vinyl ethers carrying a palladium-coordinating nitrogen auxiliary. Traditional or microwave-assisted hydrolysis of the initially formed di- or triarylated products liberates the corresponding polyaromatic carbonyl compounds.

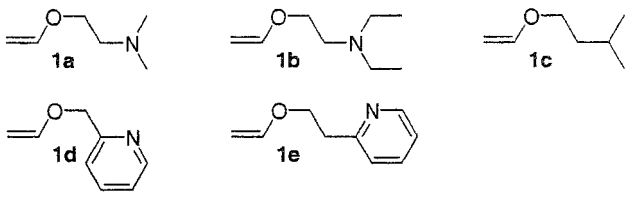
(1) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Jeffery, T. In *Advances in Metal-Organic Chemistry;* Liebeskind, L. S., Ed.; JAI Press Inc: Greenwich, 1996; Vol. 5, p 153. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (f) Larhed, M.; Hallberg, A. In *Handbook of Organo-Palladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, in press.

(2) For examples of terminal diarylation of electron-poor olefins, see: (a) Cacchi, S.; Palmieri, G. *Synthesis* **1984**, 575. (b) Sugihara, T.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 5547. (c) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (d) Bagnell, L.; Kreher, U.; Strauss, C. R. *Chem. Commun.* **2001**, *1*, 29.

(3) Heumann, A. In *Stereochemistry of Organometallic and Inorganic Compounds*; Zanello, P., Ed.; Elsevier: New York, 1994; Vol. 5; pp 557−623. (b) Negishi, E.; Copéret, C.; Liou, S. Y.; Liu, F.; Ma, S. *Chem. Rev.* **1996**, *96*, 365. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z. Y.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (d) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, 447.

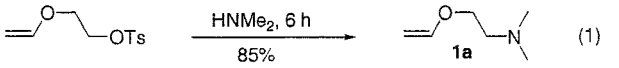
10.1021/ja011019k CCC: $20.00
Published on Web 08/04/2001

Chart 1



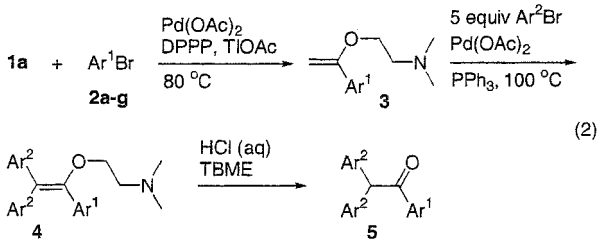
Results

The arylation studies were performed with three different vinyl ethers; (2-ethenyloxyethyl)dimethylamine, **1a**, (2-ethenyloxyethyl)diethylamine, **1b**, and isoamyl vinyl ether, **1c** (Chart 1). The first (**1a**) and the third olefin (**1c**) were prepared readily by transetherification reactions starting from ethyl vinyl ether.[4a,9] Alternatively, **1a** was prepared by a nucleophilic substitution reaction (eq 1). The diethylamino analogue **1b** was commercially available.



α-Arylation Experiments. Our strategy for α,*β*,*β*-triarylation, α,*β*-diarylation, and *β*,*β*-diarylation was partially dictated by the desire to avoid extensive purification of intermediate products. Heck protocols are available to selectively introduce the first aryl substituent in either the internal[8] (α-) or the terminal[4] (*β*-) position. Furthermore, preliminary experiments proved that arylation at the internal α-position of substrates, having the first aryl substituent attached at the *β*-position, could not be effected in useful yields. Accordingly, for the α,*β*,*β*-triarylation (eq 2) and α,*β*-diarylation (eq 3) reactions we chose to first introduce the α-substituent. It was found that the aryl bromide/thallium acetate[8,10]/DPPP (1,3-bis(diphenylphosphino)propane) or aryl triflate/DPPP combination provided the most convenient α-arylation procedures, while reactions with silver salts as halide abstractors were nonselective and sluggish.[8] The requisite α-arylated vinyl ethers **3a-i** were obtained in good yields through reaction with a slight excess of the vinyl ethers **1a**−**c** in DMF at 80 °C and in the presence of 1−5% palladium catalyst, essentially following the procedure developed by Cabri et al. (eq 2).[1c,8] Since the α-arylated compounds are highly acidic and moderately air-sensitive,[11a] they were purified by only organic/aqueous workup (except for **3a**, **3h** and **3i**) and thereafter immediately subjected to the multiarylations.

α,*β*,*β*-**Triarylation Experiments.** Triarylated vinyl ethers were obtained when the mono-α-arylated substrates (**3a**−**g**) were reacted with a 5-fold excess of aryl bromide in the presence of the palladium catalyst at 100 °C for 48 h (eq 2, Table 1). Reactions employing even larger excess of the arylating agents **2** did not lead to improved yields but only to a slightly reduced tendency for phenyl group migration.[11a,12] Palladium acetate (6%) and triphenylphosphine (PPh_3) (12%) were found to be the precatalysts of choice. In addition, an extra portion of palladium acetate (6%) was routinely added after 18 h. Biaryl formation by homocoupling of the aryl bromides **2** was one notable side-reaction in these multiarylations.[11] Attempts to substitute potassium carbonate and sodium acetate with other bases made the reaction more sluggish. Likewise, prolonged reaction times did not result in any general improvement since the catalyst slowly decomposed, leading to no further conversion of the vinyl ether. After 48 h the reactions were interrupted, and the crude triarylated vinyl ethers were purified by chromatography on alumina. In the multiarylation reactions, the dimethylamino tag[7d,13] facilitated rapid and efficient chromatography. Finally, **4a**−**j** were hydrolyzed with a *tert*-butylmethyl ether (TBME)/HCl (aq) system, and ketones **5a**−**j** were isolated.



The isolated yields in Table 1 are cumulative and thus correspond to the four-step transformation of the starting aryl halides **2** into the carbonyl products **5**. With bromobenzene as the second arylating agent, good overall yields of products could be obtained (entries 1−4). Subtle electronic factors were, however, found to be of importance for triarylation. The enol ether substrates **3e** and **3f**, carrying mesomerically electron-withdrawing α-aryl substituents, gave substantially lower yields (entries 5−6). The reaction was also sensitive to the electronic properties of the second arylating agent. Thus, the use of *p*-bromoanisole resulted in a low yield of triarylation product (entry 7). The product mixture in this case contained large amounts of *β*-phenylated compounds (aryl scrambling[11a,12]). Unexpectedly, several isomeric dimethoxybiphenyls were identified as deduced by GC−MS. A smoother transformation was encountered with *p*-tolylbromide as arylating agent, and here the yields could be improved from 59 to 76% by employing tri(*p*-tolyl)phosphine as ligand instead of PPh_3 (no loss of product caused by aryl−aryl scrambling and easier purification, entry 8). Furthermore, electron-withdrawing aryl substituents in both the substrate and in the arylating agent gave inferior yields (entry 9). In fact, the reaction of 4-acetylbromobenzene with the 4-acetylphenyl-substituted substrate **3e** yielded no triaryl-substituted product. Only diarylated product was formed in low yield (22%). To assess steric factors in the triarylation process the *ortho*-methylated substrate **3g** was reacted with *o*-tolyl bromide (Table 1, entry 10). This reaction furnished only a very low yield (7%) of the triarylated product. The diarylated ketone product **7g** was instead obtained after subsequent

(4) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Larhed, M.; Andersson, C. M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212. (c) Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285.

(5) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603. (b) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129.

(6) Arai, I.; Daves, G. D., Jr. *J. Org Chem*. **1979**, *44*, 21.

(7) Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063. (b) Pellissier, H.; Michellys, P. Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 10733. (c) Krafft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem.* **1998**, *63*, 1748. (d) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (e) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043. (f) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544.

(8) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.

(9) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.

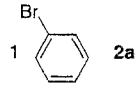
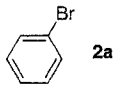
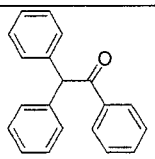
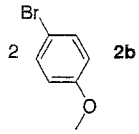
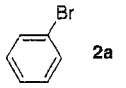
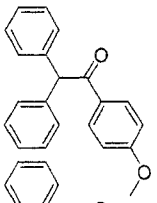
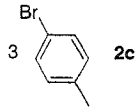
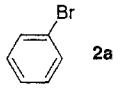
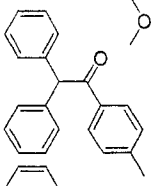
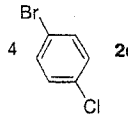
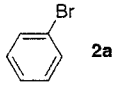
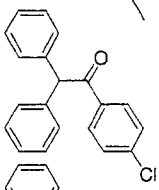
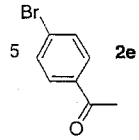
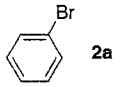
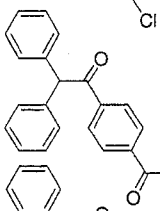
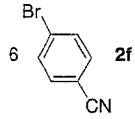
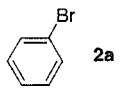
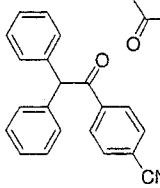
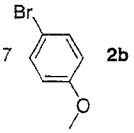
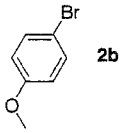
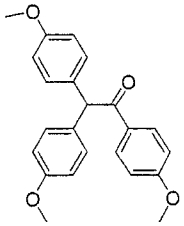
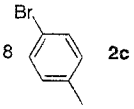
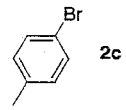
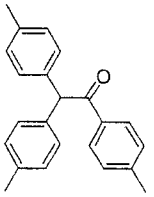
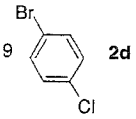
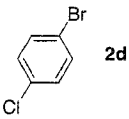
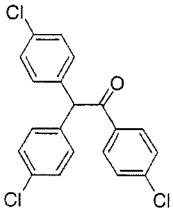
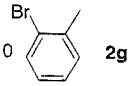
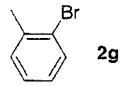
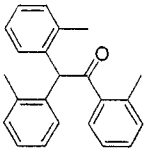
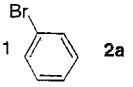
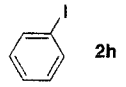
(10) Thallium(I) salts have been introduced and proved to be very useful in Pd-catalyzed reactions. Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, 31, 6573.

(11) Andersson, C. M.; Hallberg, A.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 3529. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(12) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576. (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441.

(13) Yoshida, J.; Itami, K.; Mitsudo, K.; Suga, S. *Tetrahedron Lett.* **1999**, *40*, 3403.

Table 1. Chelation-Accelerated Palladium-Catalyzed Triarylation of Vinyl Ether **1A** and Subsequent Hydrolysis

Entry	Ar^1X	Ar^2Br	Ketone	Isolated Yield (%)[a]
1	 **2a**	 **2a**		**5a** 65%
2	 **2b**	 **2a**		**5b** 66%
3	 **2c**	 **2a**		**5c** 45%
4	 **2d**	 **2a**		**5d** 50%
5	 **2e**	 **2a**		**5e** 23%
6	 **2f**	 **2a**		**5f** 14%
7	 **2b**	 **2b**		**5g** 21%
8	 **2c**	 **2c**		**5h** 59% (76%)[b]
9	 **2d**	 **2d**		**5i** 15%[c]
10	 **2g**	 **2g**		**5j** 7%[c]
11	 **2a**	 **2h**	no **5a**	

[a] Based on the starting material Ar^1X utilized in the α-arylation reaction. >95% purity by GC−MS. [b] Isolated yield when tri(*p*-tolyl)phosphine was used as ligand. [c] The corresponding α,*β*-diarylated compounds were instead obtained in useful yields, see Table 2.

hydrolysis in 70% isolated yield (see Table 2, entry 8). Unfortunately, substantial triarylation occurred exclusively with aryl bromides, and iodobenzene failed to participate in useful arylation reactions involving **6a** under the present reaction conditions (entry 11). Only a diarylated product and no triarylation product (<1% **4a**) was detected with iodobenzene, and biphenyl formation was predominant. Similarly, under the investigated conditions, the use of phenyl triflate[14] as aryl-palladium precursor did not effect triarylation.

In another experiment the *N*,*N*-diethylated substrate **3h** (α-phenylated **1b**) was compared to the *N*,*N*-dimethylated olefin analogue **3a**. The former substrate reacted much more slowly with **2a** under identical conditions and, in fact, delivered less than 5% of the desired triarylated product. Instead, formation of the corresponding α,*β*-diarylated vinyl ether occurred. Analogous arylation reactions performed using the sterically similar, but nonchelating alkyl vinyl ether **3i** (α-phenylated **1c**) did not lead to any of the desired triarylation products. Instead electron-rich, neutral, and electron-poor aryl bromides all afforded low yields of α,*β*-diarylated material.

α,*β*-Diarylation Experiments. The α,*β*-diarylated vinyl ethers **6b**−**i** could be obtained in satisfactory yields by treatment of the crude α-arylated substrates (**3**) with an excess (3 equiv) of aryl halide or triflate in the presence of palladium catalyst using three different Heck-conditions (eq 3). The products were not generally isolated as enol ethers (**6**), instead they were hydrolyzed under focused microwave irradiation (5.0 min) and isolated as the corresponding ketones (**7**). The total yields of **7** in these three-step reaction sequences are summarized in Table 2. Surprisingly, after α-arylation the diarylation product **6c** was less readily synthesized from aryl bromide **2c** than the corresponding triarylation product **4**. In addition, by utilizing aqueous conditions with aryl iodides **2k** and **2l**, small amounts of triarylated products were detected (entries 1−2). These preparative findings indicate that the vinyl ethers **3** and **6** exhibit similar reactivity with respect to *β*-arylation employing electron-rich aryl bromides. Therefore a careful individual optimization of the α,*β*-reaction conditions was necessary (entries 1−3, Table 2). The same sort of electronic effects and substrate dependence as in the triarylation appeared to be operating. Thus, problems with undesired triarylation reactions were not experienced with the electron-poor aryl substrates **2f**, **2m**−**o**, and high reaction temperatures afforded **6d**−**g** in fair yields (entries 4−7). Alternatively, employing the reaction conditions utilized for triarylations (eq 2) but with less reactive aryl bromides (5 equiv), not prone to triarylation, led to successful α,*β*-diarylations (Table 2, entries 8−9). For example, the *o*-tolyl analogue **7h** (entry 8) was isolated in 70% yield from reactions conducted according to the conditions employed in eq 2. Interestingly, *β*-arylation

(14) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 2112.

Table 2. Chelation-Accelerated Palladium-Catalyzed α,β-Diarylation of Vinyl Ether **1**A and Subsequent Microwave-Assisted Hydrolysis

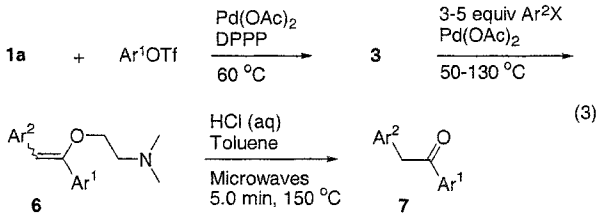
Entry	Ar^1X	Ar^2X	Time[a] (h)	Temp[a] (°C)	Ketone	Isolated Yield (%)[b]
1	**2i**	**2k**	37	50	**7b**	52
2	**2i**	**2l**	72	50	**7c**	45
3	**2i**	**2c**	13	105	**7c**	49
4	**2i**	**2m**	4	105	**7d**	38
5	**2i**	**2n**	5	100	**7e**	50
6	**2j**	**2f**	5	100	**7f**	43
7	**2i**	**2o**	72	130	**7g**	47
8	**2g**	**2g**	48	100	**7h**	70[c]
9	**2d**	**2d**	44	100	**7i**	54[c]

[a] In the β-arylation step, time and temperature were optimized to achieve maximum conversion of **3** without producing triarylated **4**. [b] Based on the starting material Ar^1X utilized in the α-arylation reaction. >95% purity by GC−MS. [c] Entries 8−9 were performed according to the conditions used in the triarylation reactions.

reactions with aryl triflates delivered only one isomer of the diarylated enol ether product (entries 4−6).

The impact of the size of the alkyl amino substituent was also examined. A switch from dimethyl (**3a**) to diethyl (**3h**) substituent suppressed triarylation at 100 °C, but the reaction was slow and not all **3h** was consumed (see α,β,β-Triarylation Experiments). To our disappointment the triarylation process started at temperatures above 100 °C. In only one exceptional reaction, the phenylation of **3h** with **2a** under triarylation conditions, a very efficent α,β-phenylation was realized (59% yield of 1,2-diphenylethanone **7a** after microwave hydrolysis). It is worth stressing that the nonchelating reference olefin **3i** was a poor substrate for the α,β-transformation, and was not readily diarylated under any of the investigated conditions.

In the early attempts to develop an efficient protocol for α,β- and α,β,β-arylation we experienced an inverse relationship between product formation and hydrolysis of **3**. The question arose, could the hydrolysis product *N*,*N*-dimethylethanolamine poison the active palladium catalyst? In an attempt to answer this question 0.2 equiv of *N*,*N*-dimethylethanolamine were added in the second arylation step in the reaction depicted in entry 2, Table 2, to examine the impact on the yield and reaction rate. The reaction was strongly suppressed (~10% conversion after 72 h). Therefore, when water was used as an additive in the α,β-arylation reactions, the temperature was kept below 80 °C to prevent extensive hydrolysis of **3** and formation of the free amino alcohol. To circumvent this problem with the triarylation reactions, an extra amount of palladium was routinely added after 18 h in the β,β-arylation step (Table 1).



β,β-Diarylation Experiments. The β,β-diaryl vinyl ethers could be prepared by a second chelation-controlled β-arylation of monoarylated **8** using aryl iodides, or an electron-poor aryl bromide (eq 4). The preparative results are summarized in Table 3. Since β-phenylated side products were formed in the presence of PPh_3 due to aryl scrambling,[12] ligandless[1e] reaction conditions employing aqueous DMF[1e,15] became the preferred methodology. The use of only a small excess of the second arylating reactant was required to obtain the β,β-diarylated products in good yields. Eight β,β-couplings were performed to verify the generality of the procedure. As apparent from the Table 3 the β,β-arylation seems less sensitive to electronic factors when compared to the corresponding triarylation (entries 5−8).

The dimethylamino functionality enabled simple and rapid column chromatography, and all Heck-products **9a**−**g** were characterized and isolated in useful yields. It is notable that in most cases arylation of **8** occurred almost exclusively at the sterically hindered β-carbon, and only a small fraction, if any, of α,β-products **6** were observed (Table 3). The results from entry 4 show that the chelation-controlled process provides the same chemoselectivity as observed with standard Heck couplings, and substitution of the iodo group occurs exclusively.[1a] However, in entries 2 and 5 small amounts of α,β isomers were observed (7 and 10% respectively). The β,β-diaryl vinyl ethers were found to be resistant to all attempts to introduce a third aromatic group in the α-position using Heck methodologies. Thus, despite additions of large excesses of the arylating agent, no α-arylation occurred. The E/Z ratios of the products **9** were

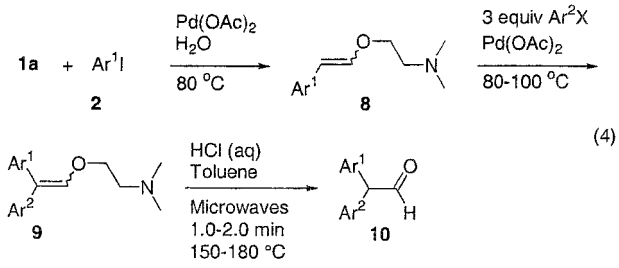
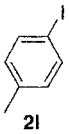
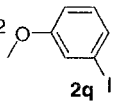
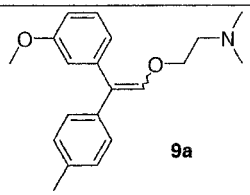
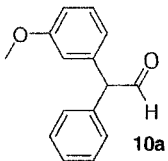
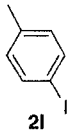
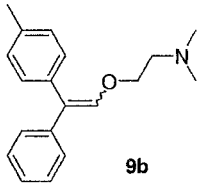
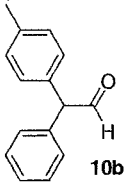
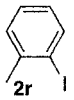
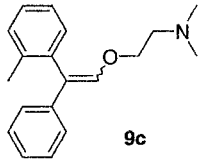
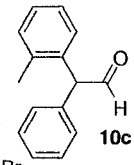
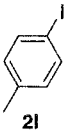
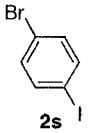
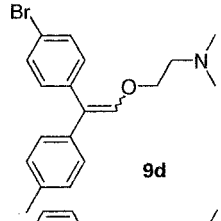
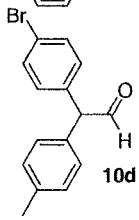
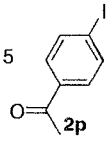
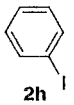
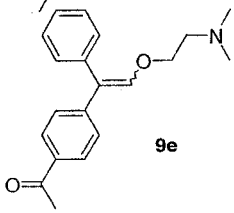
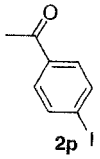
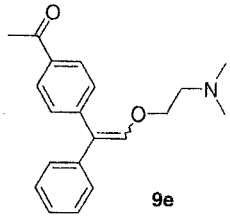
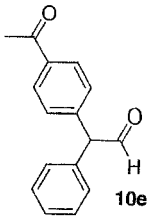
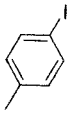
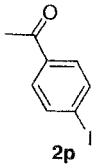
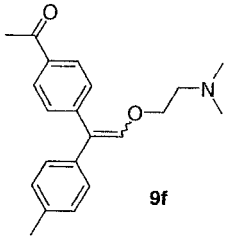
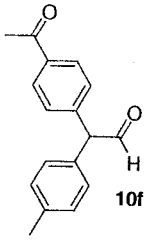
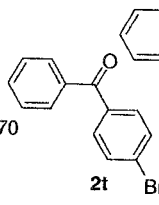
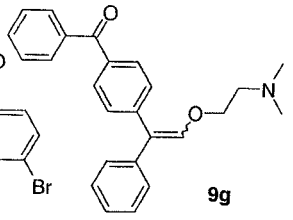
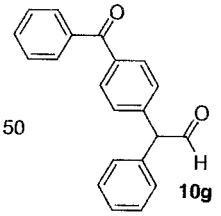


Table 3. Chelation-Accelerated Palladium-Catalyzed β,β-Diarylation of Vinyl Ether **1**A and Subsequent Microwave-Assisted Hydrolysis

Entry	Ar^1I	E/Z[a]	Ar^2X	β,β–Diarylated Vinyl Ether	α,β/β,β[a]	E/Z[b]	Isolated Yield of **9** (%)[c]	Aldehyde	Isolated Yield of **10** (%)[d]	Temp (°C)	Time (min)
1	 **2l**	28/72	 **2q**	 **9a**	3/97	3/7	65	 **10a**	93	180	2.0
2	 **2h**	30/70	 **2l**	 **9b**	7/93	3/7	63	 **10b**	98	180	2.0
3	 **2h**	31/69	 **2r**	 **9c**	1/99	4/6	57	 **10c**	91	180	2.0
4	 **2l**	26/74	 **2s**	 **9d**	3/97	3/7	50	 **10d**	83	180	2.0
5	 **2p**	48/52	 **2h**	 **9e**	10/90	7/3	40				
6	 **2h**	33/67	 **2p**	 **9e**	1/99	2/8	36	 **10e**	80	150	1.0
7	 **2l**	27/73	 **2p**	 **9f**	3/97	2/8	37	 **10f**	80	180	2.0
8	 **2h**	30/70	 **2t**	 **9g**	1/99	3/7	50	 **10g**	82	180	2.0

[a] Determined by GC−MS and ^{1}H NMR. [b] Determined by GC−MS and NMR NOE experiments. [c] Based on the starting material Ar^1X utilized in the first β-arylation reaction as a mixture of Z and E isomers. >95% purity by GC−MS. [d] Calculated from **9**. >95% purity by GC−MS.

determined by NOESY and NOEDIFF experiments. Unfortunately, high geometrical selectivity was obtained only occasionally (entries 6 and 7). The aryl group introduced in the second step was in all cases found to prefer the Z-position. A

particularly clear example of this stereochemical trend was revealed by changing the order of arylation in the synthesis of **9e**. Thus, the geometrical outcomes were completely reversed in entries 5 and 6.

Liberation of the free aryl acetaldehydes, from the corresponding enol ethers, should extend the usefulness of the β,β-methodology in synthetic applications. Unfortunately, low yields and extensive byproduct formation were encountered when traditional homogeneous one-phase reaction conditions were investigated for the acid-catalyzed hydrolysis of the β,β-diarylated products **9**. In contrast, the sensitive diaryl aldehydes[16] were isolated in high purity and yield, utilizing a very rapid (1−2 min) two-phase microwave approach (eq 4, Table 3). The microwave-assisted flash hydrolyses of **9a**−**g** were performed conveniently, and with very high reproducibility, in a two-phase HCl (aq)/toluene reaction system using a single-mode microwave cavity.[17] Since the reaction tubes are made of microwave-transparent borosilicate glass, the irradiation energy is absorbed by the reaction mixture directly (in situ heating). The liberated, acid-sensitive diaryl acetaldehydes **10** were obtained in high yields and with high purities despite reaction temperatures of up to 180 °C. It seems likely that the protonated enol ether undergoes hydrolysis in the hot acidic aqueous phase and that the noncharged aldehyde thereafter partitions into the weakly microwave-absorbing (and nonacidic) toluene layer. After irradiation, the temperature of the mixture decreases rapidly because the reaction vessel is efficiently cooled with pressurized air in the microwave synthesizer. This methodology prevents condensation and polymerization, and despite the additional possibility of performing the two-phase hydrolysis by classic heating techniques, the fast microwave protocol was adopted because of practical convenience.

Discussion

A single aryl substituent can be introduced smoothly at either the α- or β-positions of chelating vinyl ethers **1a**−**b**.[4c] Furthermore, α-arylation of isobutyl vinyl ether (**1c**) was proven to be efficient, while combinations of certain electron-deficient arylating agents and halide additives are needed for fair β-selectivity with **1c**.[11a] Ready introduction of second and third aryl groups required the β-directing and rate-promoting effect of the palladium-coordinating dimethylamino auxiliary. We propose that the chelation-accelerated arylation of **6** proceeds as depicted in Scheme 2.

In this entropy-driven scenario, the oxidative addition complex is presented to the double bond after a nitrogen−palladium(II) pre-coordination (**11**→**12**).[4] The subsequent insertion via a six-membered palladacycle provides the chelated σ-alkyl palladium complex **13** which subsequently undergoes β-elimination to deliver the tetra-substituted olefin[18] **4** and an unstable Pd(0) precursor. Importantly, the metal coordination of the dimethylamino group is reversible (it is a catalytic process). The results from the selective β,β-diarylation experiments demonstrate that

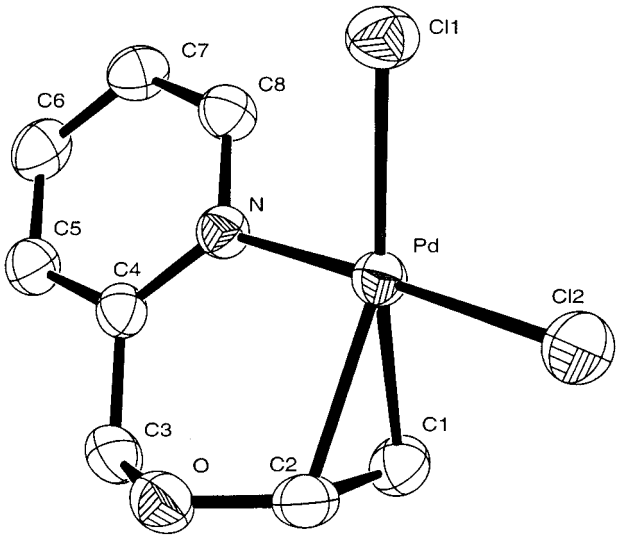
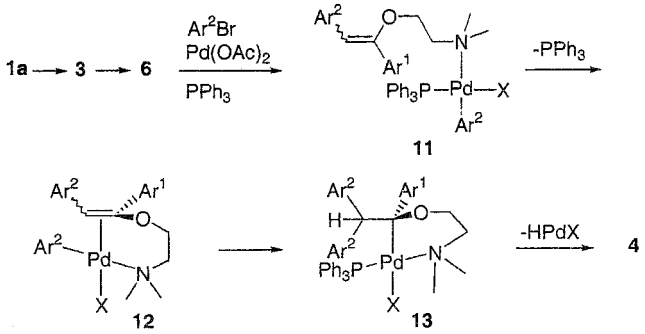


Figure 1. X-ray structure of π-complex **14**. Thermal ellipsoids are drawn at the 50% probability level.

Scheme 2



the amino auxiliary not only promotes π-complex formation/insertion but also controls the regioselectivity (Table 3).[4] The appearance of π-complexes in which the incoming palladium atom is coordinated to the dimethylamino group is supported by early work by McCrindle,[19] who isolated a $PdCl_2$-olefin complex of *cis*- or *trans*-4-methoxy-2,2,*N*,*N*-tetramethylbut-3-enylamine.

The pyridine-substituted olefin **1d**, having a two-carbon tether between the vinylic oxygen and the nitrogen atom (analogous to **1a** and **1b**), is known to undergo terminal β-arylation almost exclusively,[4b] suggesting that chelation-controlled insertion is operating. Two X-ray structures (**14** and **15**, Figures 1 and 2) of the strongly coordinating pyridine vinyl ethers **1d** and **1e** with $PdCl_2$ provide support for the involvement of N−Pd coordination[19] in the π-complex. The X-ray structures show that a ring structure with palladium is formed, and in accordance with similar reported structures,[19] there is an unsymmetrical binding between the metal and the double bond. Although, the distance between the β-carbon and the metal (2.13 and 2.17 Å) is shorter than the metal−α-carbon distance (2.22 and 2.27 Å) in the chelated complexes **14** and **15**, both olefins are predominantly β-arylated.[4b] The direction of the insertion must therefore be governed by a very powerful requirement favoring the six- or seven-membered σ-complex instead of a seven- or eight-membered σ-complex, respectively. The short bond length of the C−O bond (1.34 Å) indicates that there is a maintained orbital overlap between the alkene part and the oxygen in the

(15) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582.
(16) Ishimura, K. *Bull. Chem. Soc. Jpn.* **1941**, *16*, 293.
(17) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (b) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (c) Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596. (d) Elander, N.; Jones, J. R.; Lu, S. Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239. (e) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406.
(18) For examples of palladium-catalyzed preparations of tetra- and trisubstituted alkenes, see: (a) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331. (b) Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254. (c) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (d) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29.
(19) McCrindle, R.; Ferguson, G.; Khan, M. A.; McAlees, A. J.; Ruhl, B. L. *J. Chem. Soc., Dalton Trans.* **1981**, 986.

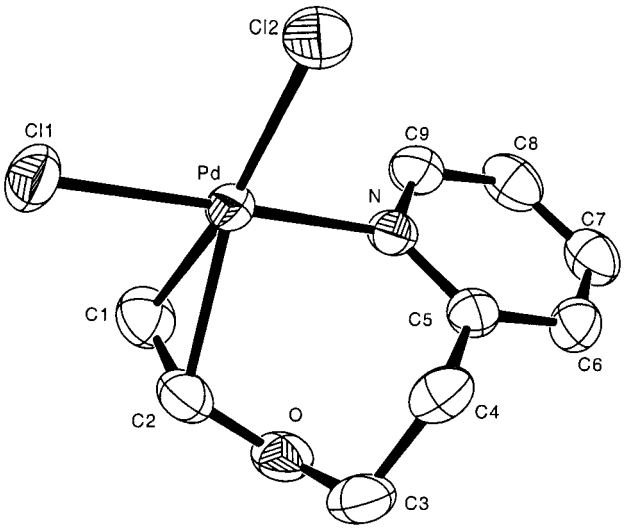
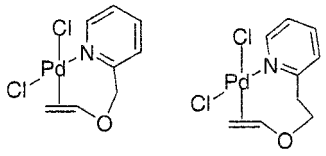


Figure 2. X-ray structure of π-complex **15**. Thermal ellipsoids are drawn at the 50% probability level.

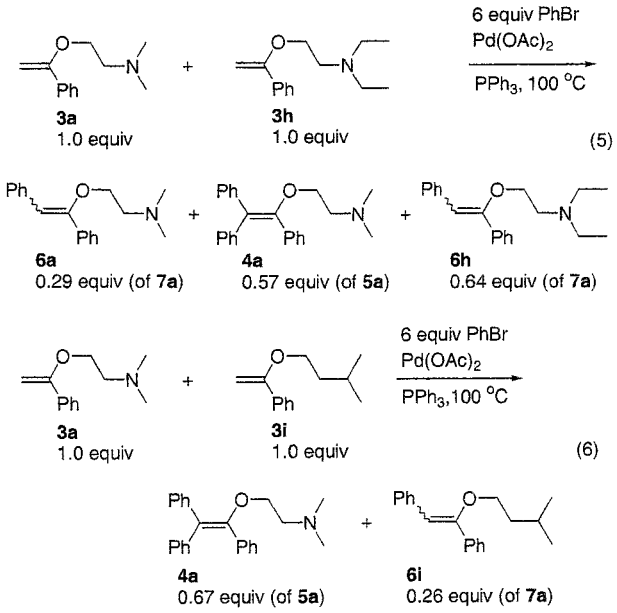
isolated complexes. This indicates that the double bond can be regarded as electron-rich even after coordination to palladium in the ring-closed system.[4a] Thus, the X-ray structures **14** and **15** imply that in prosperous reactions with the dimethylamino ethyl vinyl ethers **1a** and **8**, the regiocontrol in β- and β,β-arylation is governed by chelation-control rather than by electronic factors (e.g., an inductive effect from the oxygen).[4a] α,β-Diarylation and α,β,β-triarylation reactions starting from **1a**, should be a result of the corresponding chelation-accelerated formation of a reactive intramolecular arylpalladium π-complex. In separate arylation experiments it was found that the α-phenylated **1d** delivered neither di- nor triarylated products. This negative result might corroborate difficulties in adopting the transition-state conformation for insertion with the strongly coordinating pyridine vinyl ether system. Attempted isolation of a palladium π-complex of **1a** or the arylated counterparts (**3** or **8**) was unsuccessful, but it is anticipated that the arylpalladium π-complex **12** (Scheme 2) adopts a similar structure to X-ray structure **14**.



14 **15**

The successful introduction of the third aryl group in the unsaturated bond is much dependent on the olefin used. Thus, a minor modification such as substitution of the two amine methyl groups with two ethyl groups affords a considerably less efficient metal-presenting auxiliary. This can be attributed to unfavorable steric interactions in the transition-state for insertion, or to the fact that alkyldiethylamines, as compared to alkyldimethylamines, are poorer ligands for palladium as reported by Seligson.[20] Competitive studies revealed that the dimethylamino-tethered **3a** underwent smooth β,β-diarylation with bromobenzene in marked contrast to the much slower reactions with **3h** (eq 5) and **3i** (eq 6). In fact, **3h** did not afford any triarylated product at all, and **3i** was only partly diarylated (26% **7a** and 35% acetophenone isolated after hydrolysis).

Unfavorable steric requirements for insertion probably account for the low yield of **5j** obtained from the reaction of the



2-methylphenyl-substituted olefin **3g** with 2-methylbromobenzene (**2g**), since the 4-methyl-substituted counterparts furnished a good yield (Table 1, entries 8 and 10). Steric arguments operating prior to π-complex formation also could be applied to explain the reluctance of iodobenzene to undergo triarylation.[21] The size of the iodo atom may not allow formation of the crucial key intermediates required for insertion.[22] Alternatively, the creation of a sterically crowded, transition state encompassing "ArPdOAc" might serve as an explanation. Amatore and Jutand have shown convincingly that the arylpalladium complex, that undergoes subsequent π-complex formation, formed from iodobenzene, palladium acetate, and PPh_3 is *trans*-$Ph(PPh_3)_2PdOAc$ and not the expected *trans*-$Ph(PPh_3)_2PdI$.[23] It is presumed that this reaction is followed by an equilibrium involving *trans*-$Ph(PPh_3)_2PdOAc$, *trans*-$Ph(PPh_3)_2PdI$, iodide, and acetate.[24] Contrary to suggestions by the French researchers, with bromobenzene as substrate, *trans*-$Ph(PPh_3)_2PdBr$ is likely to predominate in the reaction-mixture since the bromide is less easily substituted by an acetate ion. To diminish the concentration of the *trans*-$Ph(PPh_3)_2PdOAc$ we attempted to conduct the reaction in absence of sodium acetate.[25] Although monoarylation, and to some degree diarylation, could be achieved with **1a**, we were unable to effect triarylation in reactions where acetate was omitted. Thus, it appears that the beneficial effect of acetate ions stabilizing Palladium(0)[25] is counteracted in cases where aryl iodides are used in sterically demanding triarylation couplings. We believe that the reluctance of the β,β-diarylated olefins **9**, even in the presence of bidentate ligands, to undergo subsequent α-arylation is a consequence of the fact that the two β-arylsubstituents impose a significant steric blockade of the double bond. An X-ray structure of *N*,*N*-dimethyl-2-[(2,2-diphenyl)ethenyloxy]ethanamine **9h** with palladium dichloride revealed a palladium-chelating dimeric struc-

(20) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520.

(21) Addition of 10% water to triarylation reactions with electron-rich aryl iodides furnished small amounts of triarylation products.

(22) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

(23) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(24) Amatore, C.; Carre, E.; Jutand, A.; Mbarki, M. A. *Organometallics* **1995**, *14*, 1818.

(25) Amatore, C.; Carre, E.; Jutand, A.; Mbarki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375. (c) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

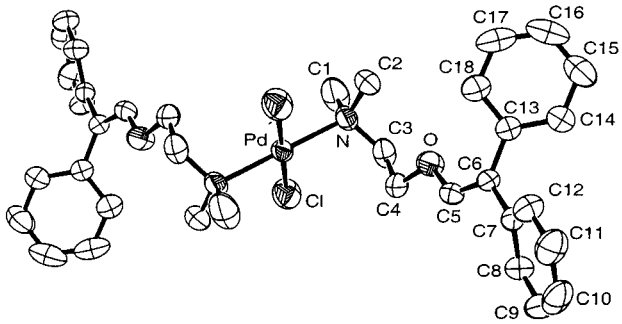
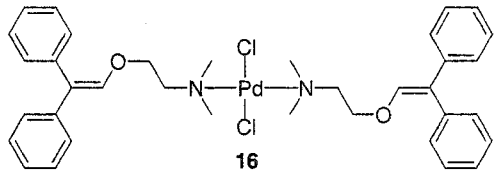


Figure 3. X-ray structure of complex **16**. Thermal ellipsoids are drawn at the 50% probability level.

ture **16** and showed that the phenyl rings in fact were locked in a "propeller" conformation[26] (Figure 3), strongly disfavoring π-complex formation/insertion.



16

Conclusions

The principle of reactivity enhancement with Heck arylation reactions for substrates containing a palladium-coordinating group by a chelation effect has now been demonstrated. Heck triarylation reactions proceeded for the first time, utilizing a catalyst-presenting auxiliary. The investigated ethyldimethylamino auxiliary has been found to (1) accelerate the reaction of the double bond by chelation-controlled delivery of the oxidative addition complex, (2) control the regioselectivity by nitrogen-directed β-arylation, (3) function as a separation tag, allowing the use of convenient purification protocols, and (4) enable rapid and efficient two-phase microwave-assisted hydrolysis. Additional work will be required to ascertain if the application of single-mode microwave irradiation also provides a general method for the promotion of palladium-catalyzed chelation-accelerated multiarylation reactions.

Experimental Section

General Procedure for Palladium-Catalyzed Triple Arylation of Vinyl Ether 1a (Table 1). α-Arylation of 1a−c Using Aryl Bromides in Syntheses of 3a−i. The reactants were dissolved or dispersed in DMF (20 mL) and added under a nitrogen atmosphere to a thick-walled tube in the following order: $Pd(OAc)_2$ (**3a**−**c**, **3g**, **3i**, 0.150 mmol, 0.0334 g; **3d**−**f**, 0.250 mmol, 0.056 g; and **3h**, 0.075 mmol, 0.0170 g, DPPP (**3a**−**c**, **3g**, **3i**, 0.330 mmol, 0.136 g; **3d**−**f**, 0.550 mmol, 0.227 g; and **3h** 0.170 mmol, 0.068 g), aryl halide (5.00 mmol), TlOAc (5.50 mmol, 1.45 g), water 1.1 mL, K_2CO_3 (6.0 mmol, 0.83 g), and vinyl ether (10.0 mmol). The tube was then closed, and the contents were magnetically stirred and heated at 80 °C for the appropriate time (**3a**−**b**, **3g**, **3i** 5 h, **3c**−**e**, **3h** 16 h and **3f** 48 h). After cooling, the reaction mixture was diluted with diethyl ether and was washed with two portions of 0.1 M NaOH. The combined aqueous phases were additionally extracted with diethyl ether. The ethereal phases were combined, washed with 10% K_2CO_3 (aq), dried with K_2CO_3 (s) and concentrated under reduced pressure until no nonarylated vinyl ether remained (GC−MS). Alternatively, products **3a** and **3j** were prepared from the corresponding aryl triflates using the methodology described in General Procedure for Palladium-Catalyzed Double α,β-Arylation of Vinyl Ethers. The α-arylated enol ethers gradually decompose[11a] and were therefore not further purified except for **3a**, **3h**, and **3i**.

***N,N*-Dimethyl-2-[(1-phenyl)ethenyloxy]ethanamine (3a).** An alumina column was used for purification of the enol ether **3a** in 92% yield (0.88 g, >95% by GC−MS, eluent: pentane/ethyl acetate (39/1) with 2% (vol) triethylamine, clear yellow oil). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.64−7.59 (m, 2H), 7.36−7.29 (m, 3H), 4.66 (d, J = 2.7 Hz, 1H), 4.21 (d, J = 2.8 Hz, 1H), 3.98 (t, J = 5.9 Hz, 2H), 2.77 (t, J = 5.8 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 160.1, 136.6, 128.6, 128.3, 125.6, 82.6, 66.5, 58.3, 46.2; MS *m*/*z* (relative intensity 70 eV) 191 (M^+, 1), 103 (16), 77 (39), 58 (100). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96: N, 7.32. Found: C, 75.65: H, 8.95: N, 7.15.

β,β-Diarylation of Crude 3. Synthesis of 4. A thick-walled tube was charged under a nitrogen atmosphere with the crude α-product **3** (∼5 mmol), $Pd(OAc)_2$ (0.300 mmol, 0.067 g), PPh_3 (0.600 mmol, 0.157 g), aryl bromide (25.0 mmol), NaOAc (5.0 mmol, 0.41 g), K_2CO_3 (25 mmol, 3.5 g) and DMF (20 mL). An extra addition of $Pd(OAc)_2$ (0.30 mmol, 0.067 g) after 18 h was routinely performed. After heating with stirring at 100 °C for 48 h the tube was cooled, and a portion of diethyl ether was added. The organic mixture was transferred to a separatory funnel and washed twice with 0.1 M NaOH. Additional extraction of the aqueous phases was performed with diethyl ether. The combined organic portions were thereafter washed with brine, dried with K_2CO_3-(s) and evaporated under reduced pressure. Finally, the residue (**4**) was purified by chromatography as described for the individual compounds.

1,1,2-Triphenylethanone (5a, Table 1). An alumina column was used for purification of the intermediate triphenylated enol ether **4a** (yellow oil, eluent: pentane/ethyl acetate (39/1) with 2% (vol) triethylamine). In addition, a pre-fraction of enol ether **6a** was isolated (0.080 g, 6%). The ketone **5a** was obtained after hydrolysis with 6 M HCl/TBME (24 h) and preparative straight-phase HPLC in 65% yield (0.86 g, >95% by GC−MS, eluent: hexane/ethyl acetate (99/1)). Alternatively, the triphenylated enol ether **4a** was further purified with a second alumina column (pentane/ethyl acetate (39/1) with 2% (vol) triethylamine) in 65% yield (1.12 g, >95% by GC−MS, white crystals). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34−7.14 (m, 10H), 7.08−7.03 (m, 3H), 6.98−6.94 (m, 2H), 3.70 (t, J = 6.1 Hz, 2H), 2.50 (t, J = 6.1 Hz, 2H), 2.15 (s, 6H); ^{13}C NMR 152.2, 141.3, 141.0, 135.5, 131.3, 130.2, 129.8, 129.7, 127.8, 127.7, 127.6, 126.3, 125.9, 125.8, 68.2, 58.5, 45.7; MS *m*/*z* (relative intensity 70 eV) 343 (M^+, 1), 165 (5), 72 (100). High-Resolution MS calcd for $C_{24}H_{25}NO$: M^+ 343.1936, Found: 343.1938.

General Procedure for Palladium-Catalyzed Double α,β-Arylation of Vinyl Ether 1a (Table 2). α-Arylation of 1a Using Aryl Triflates. Syntheses of 3a and 3c. The reactants were dissolved or dispersed in DMF (20 mL) and added under nitrogen atmosphere to a thick-walled tube in the following order: $Pd(OAc)_2$ (0.150 mmol, 0.034 g), **1a** (10.0 mmol, 1.15 g), DPPP (0.330 mmol, 0.136 g), aryl triflate (5.0 mmol), and triethylamine (10.0 mmol). Nitrogen gas was bubbled through the solution during 1 min, the tube was closed, and the contents were magnetically stirred and heated at 60 °C for 18 h. After cooling, the reaction mixture was diluted with diethyl ether and was washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined and dried with K_2CO_3 (s). After evaporation of the solvent, the remaining oil was concentrated under reduced pressure until no nonarylated vinyl ether remained (GC−MS), yielding crude monoarylated product **3**.

β-Arylation of Crude 3. Syntheses of 6. A thick-walled tube was charged under nitrogen with the crude α-product (∼0.5 mmol) prepared from aryl triflates or aryl bromides; see: α-Arylation of **1a**−**c** Using Aryl Bromides in Syntheses of **3a**−**i**. *Aryl bromides:* $Pd(OAc)_2$ (0.030 mmol, 0.0067 g), P(*o*-tolyl)$_3$ (0.060 mmol, 0.0183 g), aryl bromide (1.50 mmol), NaOAc (0.500 mmol, 0.041 g), K_2CO_3 (1.50 mmol, 0.207 g) and DMF (3 mL). *Electron-poor aryl triflates:* $Pd(OAc)_2$ (0.030 mmol, 0.0067 g), aryl triflate (1.50 mmol), triethylamine (0.603 mmol, 0.061 g) and DMF (5 mL). *Aryl iodides:* $Pd(OAc)_2$ (0.015 mmol, 0.0034 g), aryl iodide (2.50 mmol), NaOAc (0.600 mmol, 0.049 g), K_2CO_3 (0.600 mmol, 0.083 g), LiCl (1.00 mmol, 0.042 g), H_2O (0.300 mL) and DMF (2.7 mL). The tube was closed and the contents were

(26) Schmittel, M.; Keller, M.; Burghart, A.; Rappoport, Z.; Langels, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 869. (b) Rochlin, E.; Rappoport, Z. *J. Org. Chem.* **1994**, *59*, 3857. (c) Biali, S. E.; Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 846. (d) Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1997**, *30*, 307.

magnetically stirred and heated according to Table 2. After cooling, the reaction mixture was diluted with diethyl ether and was washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined, dried with K_2CO_3 (s), and concentrated under reduced pressure.

General Procedure for Microwave-Assisted Hydrolysis of α,β-Diarylated Vinyl Ether 6. After evaporation of the solvent the crude **6** was mixed with 0.25 mL of water, 0.25 mL of concentrated HCl, and 1.0 mL of toluene in a Smith process vial. The vial was sealed and positioned in the microwave synthesizer. After microwave irradiation at 150 °C for 5 min the reaction mixture was cooled and carefully neutralized with 2 M NaOH and extracted with diethyl ether. After drying with K_2CO_3 (s) and evaporation of the solvent, silica column chromatography (eluent isohexane/diethyl ether) yielded the ketone product **7** as white crystals (see Table 2).

2-(4-Acetylphenyl)-1-phenylethanone (7d, Table 2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.34 (m, 9H), 4.35 (s, 2H), 2.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 196.8, 140.1, 136.4, 135.9, 133.6, 129.9, 128.9, 128.8, 128.6, 45.4, 26.7 MS (70 eV) *m*/*z* (relative intensity) 238 (M^+,1), 105 (100), 77 (25).

General Procedure for Palladium-Catalyzed Double β,β-Arylation of Vinyl Ethers (Table 3). First β-Arylation. Syntheses of 8. The reactants were dissolved or dispersed in DMF (28 mL) and added under nitrogen to a thick-walled tube in the following order: 4-iodobenzene or 4-iodotoluene or 4-iodoacetophenone (7.0 mmol), **1a** (14.0 mmol, 1.61 g), $Pd(OAc)_2$ (0.210 mmol, 0.047 g), NaOAc (8.4 mmol, 0.69 g), LiCl (14 mmol, 0.59 g), K_2CO_3 (8.40 mmol, 1.16 g), and water (3.0 mL). The tube was closed, and the contents were magnetically stirred and heated at 80 °C overnight. The reaction was interrupted when GC−MS analysis showed that the starting aryl iodide was consumed. After cooling, the reaction mixture was diluted with diethyl ether and was washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined and dried with K_2CO_3(s). After evaporation of the solvent the remaining yellowish oil was concentrated under reduced pressure until no nonarylated vinyl ether remained (GC−MS).

Second β-Arylation. Syntheses of 9. The reactants were dissolved or dispersed in DMF (24 mL) and added under nitrogen to a thick-walled tube in the following order: aryl iodide or aryl bromide (8.4 mmol), crude β-monoarylated product (∼7 mmol), $Pd(OAc)_2$ (0.210 mmol, 0.047 g), NaOAc (8.4 mmol, 0.69 g), LiCl (14 mmol, 0.59 g), K_2CO_3 (8.40 mmol, 1.16 g), and water (3.0 mL). The tube was then closed, and the contents were magnetically stirred and heated for 1−3 days (**9a** 24 h, **9b** 24 h, **9c** 22 h, **9d** 50 h, **9e** 70 h, **9f** 48 h, **9g** 44 h). The reaction was interrupted when GC−MS analysis showed no further improvements in **9/8** ratio. After cooling, the reaction mixture was diluted with diethyl ether and was washed twice with 0.1 M NaOH. The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined and dried with K_2CO_3(s). After evaporation of the solvent and silica column chromatography (eluent EtOAc/Et_3N, 9/1) the product was obtained as a yellow/brown viscous oil.

***N,N*-Dimethyl-2-[2-(3-methoxyphenyl)-2-(4-methylphenyl)ethenyloxy]ethanamine (9a, Table 3).** Compound **9a** was obtained in 65% yield as an E/Z mixture. ^{1}H NMR (400 MHz, $CDCl_3$, E/Z = 3/7). δ 7.32−6.74 (m, 8H), *E* 6.49 (s, 0.3H), *Z* 6.46 (s, 0.7H), 4.00 (t, J = 6.2 Hz, 2H), 3.76 (s, 3H) 2.63 (t, J = 6.2 Hz, 2H), 2.33 (s, 3H), 2.29 (s, 6H). MS (70 eV) *m*/*z* (relative intensity) 311 (M^+, 4), 72 (100), 58 (58). Anal.calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09. Found: C, 76.91; H, 8.01.

General Procedure for Microwave-Assisted Hydrolysis of β,β-Arylated Products 9. The enol ether **9** was placed in a Smith process vial together with 0.25 mL of water, 0.25 mL of concentrated HCl and 1.0 mL of toluene. The tube was sealed and positioned in a Smith synthesizer rack. After microwave irradiation at 150 or 180 °C for 1−2 min (see Table 3) and subsequent cooling the reaction mixture was carefully neutralized with 2 M NaOH and extracted with diethyl ether. After drying with K_2CO_3(s) and evaporation of the solvent the crude aldehyde **10** was obtained as a yellow oil (> 95% pure by GC−MS). NMR and IR spectra were quickly recorded on these air- and light-sensitive compounds.

2-(3-Methoxyphenyl)-2-(4-methylphenyl)ethanal (10a, Table 3). The enol ether **9a** (0.061 g) yielded after hydrolysis the diarylated aldehyde **10a** (0.044 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (d, J = 2.5 Hz, 1H), 7.4−6.6 (m, 8H), 4.82 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H) 2.36 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 160.1, 138.1, 137.5, 133.2, 129.8, 129.1, 121.5, 115.2, 112.9, 63.8, 55.4, 29.8, 21.2; MS (70 eV) *m*/*z* (relative intensity) 240 (16, M^+), 211 (100), 196 (25). IR ($CDCl_3$) 1724 cm^{-1}. High-resolution MS calcd for $C_{16}H_{16}O_2$: $[M + H]^+$ 241.1228, Found: 241.1228.

Acknowledgment. We thank the Swedish Natural Science Research Council, and the Swedish Foundation for Strategic Research for financial support. We also thank Personal Chemistry AB for supplying the microwave equipment and Dr. Mikael Hedeland and Jonas Höwing for help with HRMS and X-RAY, respectively. Finally, we thank Dr. Boris Smith and Dr. Carl-Magnus Andersson for intellectual contributions to this project.

Supporting Information Available: Experimental procedures, spectroscopic and analytical data for all new compounds (PDF) and X-ray crystallographic data, in CIF format, are available. This material is available free of charge via the Internet at http://pubs.acs.org.

JA011019K