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Chelation-Controlled, Palladium-Catalyzed Arylation of Enol Ethers with Aryl Triflates. Ligand Control of Selection for α- or β-Arylation of [2-(Dimethylamino)ethoxy]ethene.

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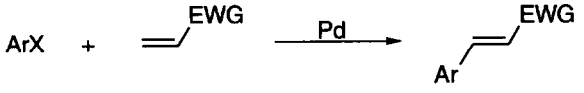
Abstract: Palladium-catalyzed arylation reactions of [2-(Dimethylamino)ethoxy]ethene (**1**) with a series of aryl triflates were performed under a variety of reaction conditions. In particular, the influence of phosphine ligands and halide additives on regioselectivity were studied. It was found that the chelation-controlled arylation of **1** affords an expedient route for the conversion of phenols into arylacetaldehydes. Alternatively, the same starting materials could be used to synthesize acetophenones by reversing the regioselectivity with bidentate phosphine ligands.

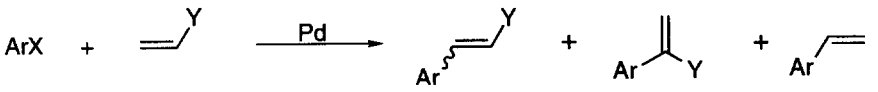
INTRODUCTION

Palladium-catalyzed arylation reactions of olefins carrying electron-withdrawing groups lead to the corresponding terminally arylated products in useful yields[1] (Equation 1). Unfortunately, other important classes of olefins, such as 1-alkenes and heterosubstituted olefins, have proven less useful as substrates for this type of transformation. This fact seriously limits the applicability of this robust method of carbon-carbon bond formation. Major complications associated with the latter type of substrates include cleavage of the hetero substituent and, particularly, low regioselectivity[2] (Equation 2). Modifications of the reaction conditions, catalyst systems or the substrates themselves have provided procedures permitting the arylation of some heterosubstituted olefins, for example vinyl imides[3,4], amides[4] and silanes.[5] Successful Heck-type arylation has also been reported for vinyl sulfides[6], vinylphosphonates[7] and certain nitrostyrenes.[8]



(1)

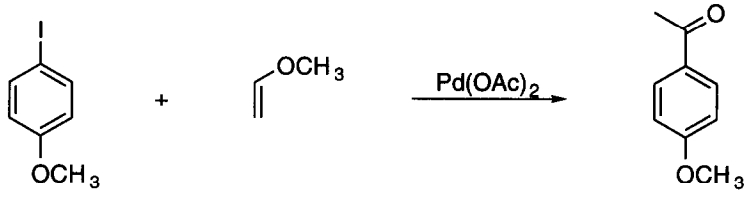
EWG = COOMe, CN, Ph etc.



(2)

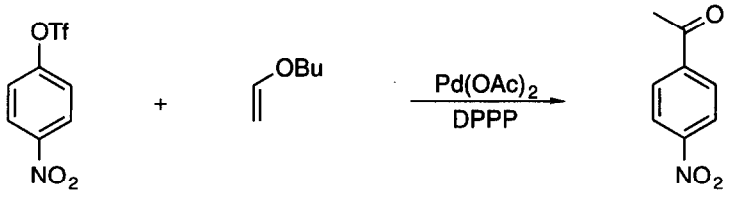
Y = Heteroatom

We have been interested in developing methods for the selective, palladium-catalyzed terminal (β-) substitution of enol ethers. These substrates have been shown to undergo apparently electronically controlled substitution, thus delivering primarily the branched (α-) arylated products, particularly when electron-donating substituents are present also in the aromatic reaction partner.[2] For example, 4-methoxyacetophenone is the only isolable product from 4-methoxy-1-iodobenzene and methyl vinyl ether[9] (Equation 3).

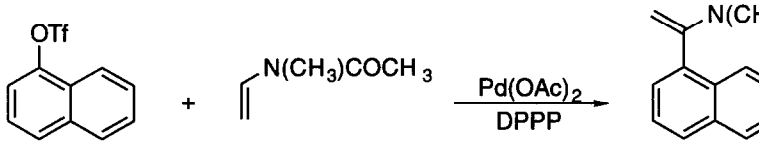


55% (3)

Phosphine ligands were also found to promote α-selectivity.[2,9] More recently, Cabri and co-workers have developed a very useful procedure for the selective α-arylation of vinyl ethers, which relies on bidentate phosphine ligands, sometimes in combination with silver or thallium additives.[4,10] This procedure has been successfully applied also to electron-deficient arylating agents (Equation 4) as well as to other heterosubstituted olefins[4] (Equation 5).

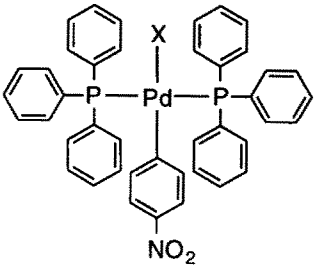


54% (4)



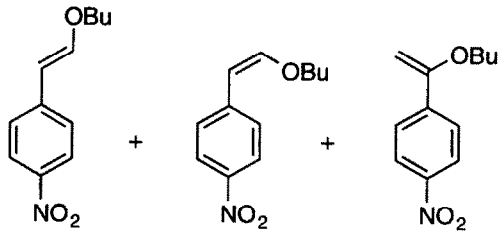
87% (5)

We have reported further that the regioselectivity is not only governed by aryl substituents and palladium ligands, but also by the nature of the counter ion in the oxidative addition complex.[11a] Thus, in stoichiometric reactions starting from bis(triphenylphosphino)-4-nitrophenyl palladium halides, a much higher β-selectivity was observed (β/α = 10) with the chloride complex (Equation 6) than with the corresponding bromide or iodide species (β/α = 4 and 1, respectively). A similar regiochemical trend was evident for the series of simultaneously formed phenylated products, derived from aryl interchange within the phosphine complexes[11] (Equation 6). The addition of salts (LiCl, LiBr, LiI, Bu_4NCl, Bu_4NBr, Bu_4NI) to catalytic reactions employing 4-nitrophenyl triflate further substantiated the influence of counterions on the regioselectivity of the arylation reaction[12] (Equation 7). For preparative purposes we turned to aroyl chlorides as precursors to "arylpalladium chlorides". These arylating agents provided the desired β-arylated products with reasonable regioselectivity[13] (Equation 8). Under slightly modified conditions carbonyl extrusion from the intermediate aroylpalladium chloride complex could be suppressed, leaving an entry to semimasked 1,3-dicarbonyl compounds employing very similar chemistry[14] (Equation 9). Interestingly, the latter transformation provided exclusively the β–substituted products.

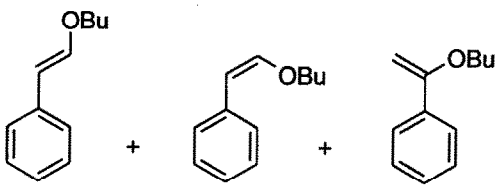


+ 

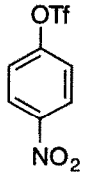
Et_3N → (6)



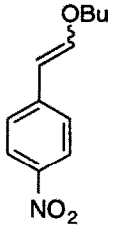
X=Cl	28%	13%	4%
Br	25%	12%	9%
I	10%	10%	21%

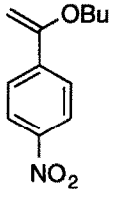


X=Cl	28%	11%	16%
Br	21%	11%	22%
I	5%	7%	47%



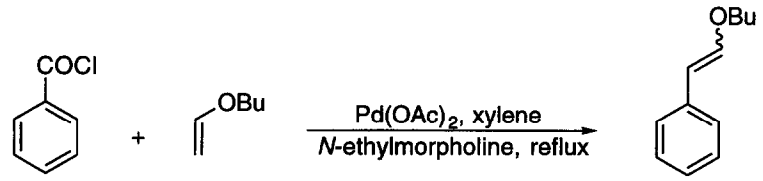
+ 

+ Halide $\xrightarrow[Et_3N]{Pd(OAc)_2}$ 

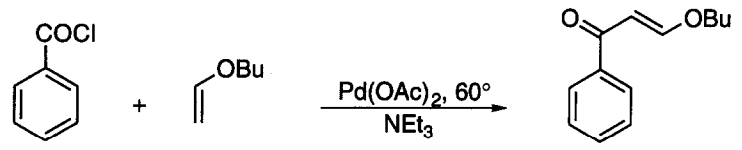
+ 

(7)

Solvent	Salt		
DMF	LiCl	13	1
DMF	LiBr	14	1
DMF	LiI	5	1
CH_3CN	Bu_4NCl	8	1
CH_3CN	Bu_4NBr	6	1
CH_3CN	Bu_4NI	3	1

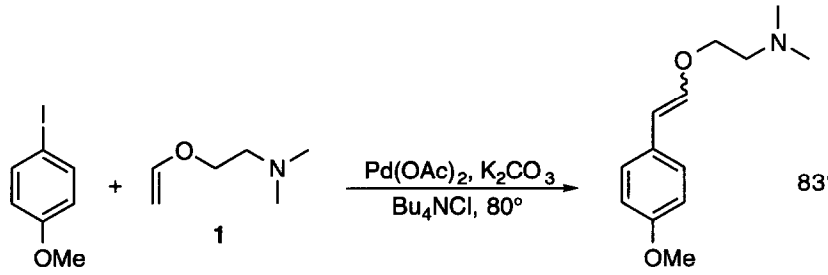


53% (8)



69% (9)

In most of the above examples, the regioselectivity was still dependent, to some extent, upon the nature of the reactants and reaction conditions. In order to achieve a more general and synthetically useful procedure for the preparation of arylacetaldehyde equivalents, we turned to modifying the vinyl ether substrate. As a result, we have recently introduced amino functionalized vinyl ethers as substrates in the Heck arylation reaction.[15] The use of such olefins allowed the transformation of aryl iodides into the corresponding arylethanals by a highly efficient, probably chelation-controlled, β-arylation process (Equation 10). An extended study, including several nitrogen-containing vinyl ethers[16] supports a mechanism involving nitrogen-palladium coordination as the regiocontrolling event.



83% (10)

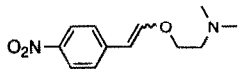
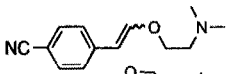
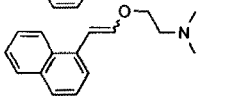
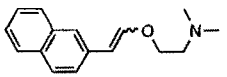
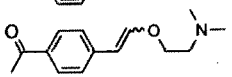
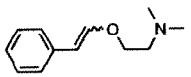
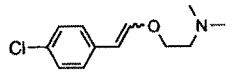
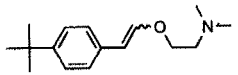
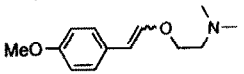
Badone and Guzzi have recently reported that a high β-selectivity is achieved in the arylation of [2-(ethenyloxy)ethyl]diphenylphosphine provided that activated triflates are used.[17] These authors reported unsuccessful results from the reaction of [2-(dimethylamino)ethoxy]ethene (**1**) with 4-acetylphenyl triflate, using phase transfer conditions.[18]

We now wish to report that both electron rich and electron deficient aryl triflates (including 4-acetylphenyl triflate) are useful in chelation-controlled arylation reactions under carefully chosen conditions. We have also found that the substrate **1** can be selectively arylated in either the α- or β-position, with equally good regiocontrol, depending upon the choice of phosphine ligand.

RESULTS

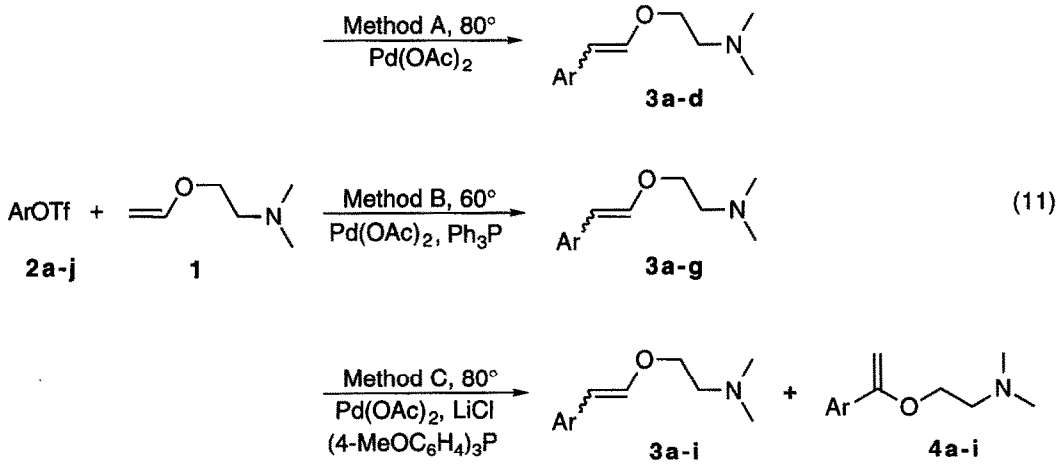
4-Nitrophenyl triflate (**2a**), which is reactive enough to undergo oxidative addition to Pd(0) in the absence of phosphine ligands, has been shown previously to arylate butyl vinyl ether with very low regioselectivity (β/α = 60/40).[12] As shown in Table I, **2a** provided a good yield of the β-arylated product **3a**, in a highly regioselective reaction, when **1** was the substrate (Equation 11; Method A).

Table I. Regioselective β-Arylation of **1** with Aryl Triflates under Various Conditions[a].

Triflate	Product		Method A			Method B			Method C			
			Time (h)	Yield[bc] (%)	(*E*)/(*Z*)[d]	Time (h)	Yield[bc] (%)	(*E*)/(*Z*)[d]	Time (h)	Yield[b] (%)	β/α[e]	(*E*)/(*Z*)[d]
4-Nitrophenyl **2a**		**3a**	6	87	50/50	4	86	50/50	22	38[f]	99/1	50/50
4-Cyanophenyl **2b**		**3b**	16	78	45/55	9	75	45/55	18	72	98/2	28/72
1-Naphthyl **2c**		**3c**	16	85	34/66	120	83	50/50	120	85	95/5	38/62
2-Naphthyl **2d**		**3d**	16	93	40/60	9	93	50/50	18	89	93/7	50/50
4-Acetylphenyl **2e**		**3e**	20[g]	73[h]	40/60	20	82	50/50	24	88	97/3	47/53
Phenyl **2f**		**3f**	72[g]	44[h]	38/62	20	95	46/54	24	90	94/6	55/45
4-Chlorophenyl **2g**		**3g**	72[g]	47[h]	34/66	20	95	43/57	47	92	93/7	44/56
4-*t*-Butylphenyl **2h**		**3h**	72[g]	22[h]	36/64	100[g]	75[h]	46/54	66	76	90/10	64/36
4-Methoxyphenyl **2i**		**3i**	72[g]	12[h]	32/68	100[g]	20[h]	47/53	47	72	89/11	45/55
2,6-Diethylphenyl **2j**			72[g]	<5[h]	-	72	0[h]	-	47	0[h]	-	-

Footnotes: [a] Reactions utilized aryl triflate (5.0 mmol), **1** (10 mmol), triethylamine (10 mmol) and palladium acetate (0.15 mmol) in 20 ml of DMF. Method A; reactions were carried out at 80 °C in the absence of added phosphine or lithium chloride. Method B; reactions were carried out at 60 °C in the presence of triphenylphosphine (0.33 mmol). Method C; reactions were carried out at 80 °C in the presence of tris(4-methoxyphenyl)phosphine (0.15 mmol) and lithium chloride (25 mmol). [b] Yield of pure (>94% by GLC-MS) isolated **3**, based on the aryl triflate. [c] The α-regioisomer was not observed. [d] (*E*)/(*Z*) mixture. Determined by GLC-MS and ^{1}H NMR. [e] The crude product was obtained as a mixture of α- and β-regioisomers. Determined by GLC-MS. [f] *N*-Methyl-*N*-(4-nitrophenyl)-2-(ethenyloxy)ethanamine was also formed. [g] No further conversion after longer reaction time. [h] Remaining unreacted triflate.

Contrary to analogous arylations utilizing aryl halides, phase transfer conditions were essentially ineffective with most triflates. The best results were obtained using triethylamine as the base. DMF was found to be superior to DMSO or acetonitrile as the solvent in our initial experiments. Under the same conditions ($Pd(OAc)_2$ catalyst; Method A) other reasonably reactive triflates (**2b-2d**) were converted smoothly also. Although reactions employing the less reactive triflates did not proceed to completion, strict regioselectivity for β-arylation was observed with all arylating agents (**2a-2i**) under these conditions, demonstrating a powerful directing effect of the dimethylaminoethyl moiety, in analogy with previous reports using aryl halides as reagents.[15]



Since inefficient oxidative addition was a probable cause for the lower reaction rate with **2e-2i**, we turned to a triphenylphosphine-ligated catalyst system (Method B, Equation 11 and Table I). Under these conditions most aryl triflates provide useful yields of arylated products **3** with the exceptions of the very electron rich 4-methoxyphenyl triflate (**2i**) and the sterically hindered 2,6-diethylphenyl triflate (**2j**). Reactions at higher temperatures with these triflates (**2i** and **2j**) did not result in higher yields. The presence of triphenylphosphine did not affect the regiochemistry of the process negatively (β/α ≈ 99/1). Despite the use of a ligand, there was a profound difference in the reaction rate (reaction times vary from 4h to 120h) with the various triflates **2a-2g**, in agreement with the assumption that oxidative addition is the rate-limiting step in most cases.[19] In the slow reaction employing the 4-methoxyphenyl triflate **2i** with Method B, a small amount of **3f** was observed in addition to the expected major product **3i**, upon GLC-MS analysis of the crude product (cf. Equation 6).

Chen and Yang[20] have reported that relatively electron rich phenyl fluoroalkanesulfonates can be used as substrates in the Heck-reaction with dichlorobis(triphenylphosphine)palladium as catalyst. Also, in our case, a catalytic system stabilized with lithium chloride[21] and tris(4-methoxyphenyl)phosphine allowed higher reaction temperature and efficient conversion also of the 4-methoxyphenyl triflate (**2i**) into **3i**. However, in this case the reaction afforded larger amounts of the undesired regioisomer **4i** (β/α = 89/11). Although Method C was effective with all triflates except **2a** and in particular **2j** (no reaction), a similar loss in selectivity was encountered in most cases, yielding product mixtures where the β/α ratio appeared to depend upon the electronic properties of the *para*-substituent (Table I). Thus, electron-withdrawing groups favoured β-selectivity whereas the electron-donating groups gave a higher proportion of the α-arylated **4**. This behaviour parallels that found in the reactions of substituted aryl halides with butyl vinyl ether, but the β/α ratios obtained from **1** are substantially higher, suggesting that the substrate **1** exerts chelation-control also using Method C.

Although Method C did not result in perfect β-selectivity, pure **3** was obtained by a careful hydrolysis of the crude product. This selective and mildly acidic workup cleaved the minor α-product, removed non basic by-products and left the β-products intact. With the particularly reactive triflate **2a** a nucleophilic displacement / de-methylation was competing with the oxidative addition complex formation. A control experiment revealed that this displacement was not palladium-promoted.

The α-selectivity in reactions of butyl vinyl ether with triflates recently has been reported to correlate with the ligand cone angle when monodentate phosphines were employed. Exclusive α-selectivity was reported with strongly coordinating phosphines such as methyldiphenylphosphine.[10a] We compared ligands representing different coordinating properties in Method B (60° C; without chloride ions) and C (80° C; with lithium chloride present). As evident from Table II, although the choice of ligand strongly influenced the conversion rate in Method B, none of them was able to impose α–selectivity. Using phenyl triflate (**2f**) none of the more sophisticated ligands showed an advantage over triphenylphosphine. The chloride-containing catalyst (Method C) again led to a lower selectivity, irrespective of the choice of ligand (Table II). As expected, this method was more efficient in terms of conversion with most of the ligands.

Table II. Influence of Ligands on the Arylation of **1** with phenyl triflate (**2f**), according to Method B or C.

Ligand			Method B[a]			Method C[a]			
	θ[b] (deg)	ν[c] (cm^{-1})	Time (h)	Yield of **3f**[d] (%)	(*E*)/(*Z*)[e]	Time (h)	Yield of **3f+4f**[f] (%)	(*E*)/(*Z*)[e]	β/α
$(4\text{-}MeOC_6H_4)_3P$	145	2066.1	120	68[h]	50/50	22	100	48/52	94/6
$(2\text{-}MeC_6H_4)_3P$	194	2066.6	72[g]	53[h]	56/44	22[g]	89[h]	38/62	95/5
$MePPh_2$	136	2067.0	120	83[h]	50/50	70	77[h]	32/68	94/6
PPh_3	145	2068.9	49	100	46/54	22	99	63/37	93/7
$(4\text{-}FC_6H_4)_3P$	145	2071.3	72[g]	64[h]	47/53	22	100	61/39	92/8
$Ph_2PC_6F_5$	158	2074.8	72	0[h]		70	60[h]	16/84	95/5
$AsPh_3$	142		72[g]	9[h]	46/54	70	8[h]	23/77	94/6
$(2\text{-furyl})_3P$			72[g]	<1[h]		22	100	41/59	93/7
none			72[g]	24[h]	38/62	70	19[h]	11/89	96/4

Footnotes: [a] Reactions utilized **1** (2 mmol), **2f** (1 mmol), triethylamine (2 mmol) and palladium acetate (0.030 mmol) in 4 ml of DMF. Method B; reactions were carried out at 60 °C in the presence of ligands (0.066 mmol). Method C; reactions were carried out at 80 °C in the presence of ligands (0.030 mmol) and lithium chloride (5 mmol). [b] Cone angle; see ref 22 and 23. [c] IR frequency of $Ni(CO)_3L$ complex; see ref 22 and 23. [d] Determined by GLC-MS. (*E*)/(*Z*) mixture. The α-regioisomer was not observed, except in the case of $(2\text{-}MeC_6H_4)_3P$ where the β/α ratio was found to be 96/4. [e] Determined by GLC-MS and ^1H NMR. [f] Determined by GLC-MS. The crude product was obtained as a mixture of α- and β-regioisomers. [g] No further conversion after longer reaction time. [h] Remaining unreacted triflate.

The most striking effect of the chloride additive and the increased reaction temperature was in the case of tri-2-furylphosphine, where a quantitative yield of arylated products (**3** + **4**) resulted using Method C despite the fact that this phosphine failed to support the reaction under the conditions of Method B. Tri-2-furylphosphine, an exceptionally good π-acceptor ligand but a weak σ-donor,[22] appears to create a Pd(0)-complex unable to give oxidative addition with **2f** when chloride ions are not present. Since our preliminary experiments indicate that the ligand/palladium (P/Pd) ratio was critical in Method C, we decided to also study the influence of a range of P/Pd ratios on reaction rate and selectivity (Table III).

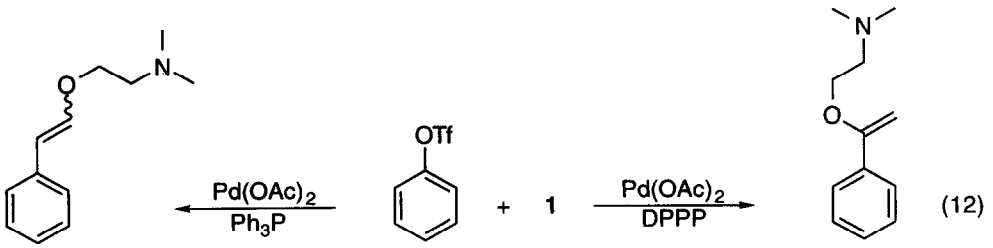
When analyzing the reaction after 16h, a P/Pd ratio of 1/1 appeared optimal with respect to both conversion and selectivity. However, conversion was virtually complete with all P/Pd ratios after 46h of reaction. In the absence of tris(4-methoxyphenyl)phosphine, the coupling reaction did not proceed to completion, indicating that chloride ions alone do not facilitate the reaction of **1** with phenyl triflate. The use of 1 equivalent rather than 2 equivalents of triethylamine resulted in almost identical β-selectivity (β/α = 95/5 and β/α = 94/6 respectively), but a slightly slower conversion.

Table III. The Influence of Ligand / Pd Ratio on the Regioselectivity of the Arylation of **1** with Phenyl Triflate (**2f**) according to Method C[a]

	Yield of **3f+4f** (%)[b]		β/α-ratio[c]	
Phosphine/Pd	16h	46h	16h	46h
0	14	19[d]	96/4	97/3
1/2	62	100	95/5	96/4
1/1	72	96	95/5	95/5
2/1	55	89	93/7	93/7
3/1	37	92	92/8	93/7
4/1	5	87	≈80/20[e]	91/9

Footnotes: [a] Reactions utilized **1** (2 mmol), **2f** (1 mmol), triethylamine (2 mmol) and palladium acetate (0.030 mmol), tris(4-methoxyphenyl)phosphine (0.00-0.12 mmol) and lithium chloride (5 mmol) in 4 ml of DMF at 80 °C. [b] Determined by GLC-MS. [c] Determined by GLC-MS and ^{1}H NMR. [d] Remaining unreacted triflate. [e] Low yield did not allow an accurate determination.

Strongly coordinating, and in particular chelating phosphine ligands impose a high selectivity for α-arylation of enol ethers and some other relatively electron-rich olefins.[4,10] Cabri and co-workers found that the selective α-arylation was particularly facile when 1,3-bis(diphenylphosphino)propane or 1,1′-bis(diphenylphosphino)-ferrocene were employed as chelating ligands.[4,10] We have established that the influence of a series of bidentate phosphines on the outcome of the arylation of **1** with **2f** is qualitatively similar (Table IV) to that observed with butyl vinyl ether. For example, the addition of 2.2 molar equivalents of DPPP (P/Pd = 4.4/1) completely reversed the regioselectivity, giving exclusively the α-arylated product **4f** in high yield (Equation 12).



3f **2f** **4f** (12)

The ligands with longer (DPPB) or shorter (DPPM[24], DPPE) tethers were less efficient in promoting α-arylation, confirming the results reported by Cabris group.[4,10] Lower P/Pd ratios produced product mixtures containing considerable amounts of the β-arylated **3f.** We were interested in evaluating the generality of the DPPP-mediated α-arylation of **1** with respect to arylating agent. Table V summarizes our results from reactions with the triflates **2a-2j** (Equation 13).

Table IV. Influence of Bidentate Phosphine Ligands on the Regiochemistry of Arylation of **1** with Phenyl Triflate (**2f**)[a].

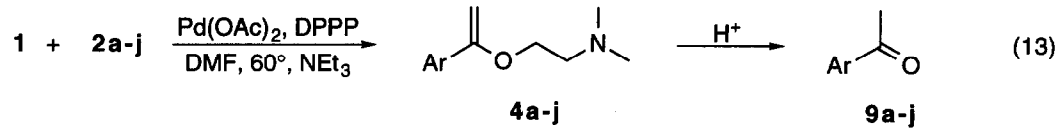
Ligand	P-Pd-P angle (deg)	Ligand/Pd[b]	time (h)	Yield of **3f** + **4f** (%)[c]	β/α[d]
$Ph_2PCH_2PPh_2$, DPPM	≈73[e]	1.1	144	18[h]	99/1
		2.2	168	14[h]	99/1
$Ph_2P(CH_2)_2PPh_2$, DPPE	≈85[e]	1.1	72	66[h]	98/2
		2.2	168	81[hi]	17/83
$Ph_2P(CH_2)_3PPh_2$, DPPP	≈90[e]	1.1	72	54[hi]	75/25
		2.2	22	100[j]	1/99
$Ph_2P(CH_2)_4PPh_2$, DPPB	≥90[f]	1.1	168	64[h]	92/8
		2.2	42	94[i]	23/77
1,1′-Bis(diphenyl-phosphino)ferrocene, DPPF	≈99[g]	1.1	72	86[i]	47/53
		2.2	22	95[j]	1/99
PPh_3		2.2	49	100	99/1
None			49[k]	23[h]	99/1

Footnotes: [a] Reactions utilized **1** (2 mmol), **2f** (1 mmol), triethylamine (2 mmol), palladium acetate (0.030 mmol) and phosphine ligand (0.00-0.066 mmol) in 4 ml of DMF at 60 °C. [b] Molar ratio between the phosphine ligand and palladium acetate. [c] Determined by GLC-MS . [d] Determined by GLC-MS and ^1H NMR. [e] See ref. 25. [f] See ref. 26. [g] See ref. 27. [h] Remaining unreacted triflate. [i] Yield of the β-regioisomers plus the methyl ketone **9f**, obtained after acidic workup. [j] Yield of the corresponding methyl ketone **9f**, obtained after acidic workup. [k] No further conversion after longer reaction time.

Table V. Arylation of **1** with Various Aryl Triflates (**2**) in the Presence of DPPP[a].

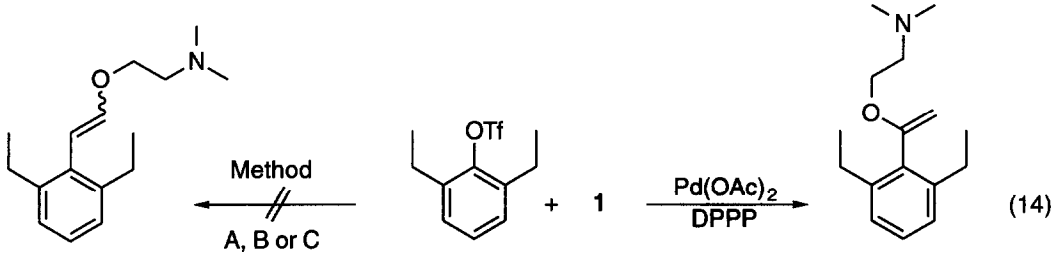
Aryl Triflate	Product[b]	Time (h)	Yield (%)[c]
2a	**4a**	40	20[def]
2b	**4b**	168	83
2c	**4c**	14	100
2d	**4d**	14	92
2e	**4e**	40	88
2f	**4f**	14	98
2g	**4g**	40	100
2h	**4h**	14	92[f]
2i	**4i**	14	98
2j	**4j**	120	80[f]

Footnotes: [a] Reactions utilized **1** (2mmol), **2** (1 mmol), triethylamine (2 mmol), palladium acetate (0.030 mmol) and DPPP (0.066 mmol) in 4 ml of DMF at 60 °C. [b] The only products of the reactions were the α-regioisomers **4** and the corresponding methyl ketones **9**. [c] GLC-MS yield of the corresponding methyl ketone **9**, obtained after acidic workup. [d] *N*-Methyl-*N*-(4-nitrophenyl)-2-(ethenyloxy)ethanamine was also formed. [e] Remaining unreacted triflate. [f] Isolated yield in 5 mmol scale of the corresponding methyl ketone **9**.



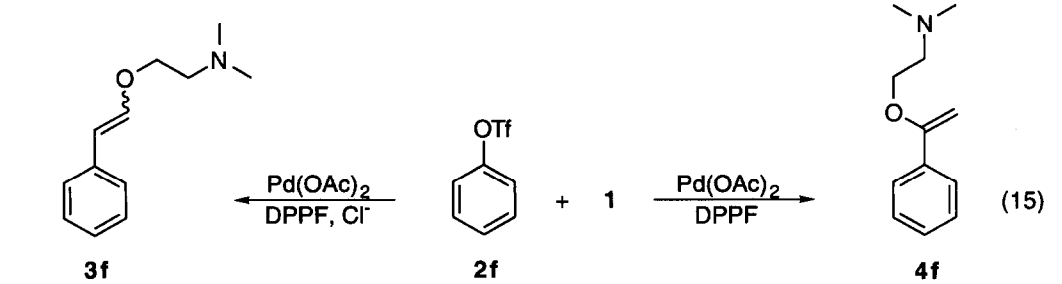
(13)

The process was found to be highly selective for α-substitution with all triflates tested, delivering the products **4a-4j** and, after acidic workup, the corresponding acetophenones (**9a-9j**). Good yields were observed with DPPP, provided the substrates were not substituted with a 4-nitro group. The bidentate ligand permitted lower reaction temperatures[28] and also 4-methoxyphenyl triflate (**2i**) reacted smoothly. It is interesting to note how the relatively facile α-arylation of **1** with **2j** contrasts the very sluggish reaction which occurs under conditions promoting the β-selective process (Equation 14). In separate experiments (Table VI), it was further shown that the α-directing capacity of DPPF as well as DPPE and DPPB could be counteracted by the addition of chloride ion to the medium. In the presence of a large excess of lithium chloride, the product distribution was reversed from a modest α-selectivity to favour the β-arylated **3f** in reactions utilizing the less efficient chelating ligands DPPE and DPPB (cf. Tables IV and VI). No effect of chloride ion upon the regioselectivity was observed when DPPP was present, but the conversion was extremely slow with this ligand.



(14)

A particularly impressive controlling role of the chloride ion was revealed using DPPF in the coupling. Thus, whereas this ligand imposed exclusive α-regioselectivity at a P/Pd ratio of 4.4 (Table IV), useful β-selective arylation to produce **3f** was encountered in the presence of chloride ion under otherwise identical conditions (Table VI, Equation 15). Both **4f** and **3f** were obtained in high yields. A further point of interest is that the bidentate ligands have to be present with a P/Pd ratio of 2.2 in order to promote α-selectivity efficiently. Although phosphine oxidation was a possible cause of the loss of selectivity using lower ratios, we were unable to improve the yields of **4f** by working under inert conditions or using hydroquinone as an antioxidant.



(15)

We had previously noted a profound influence of different halide ions on arylations of butyl vinyl ether with aryl triflates.[12] To enable an adequate comparison of the influence of halide additives we selected 2-naphthyl triflate (**2d**) as a suitable precursor (Table VII) since the parent compound phenyl triflate was considerably less reactive.

We observed that only activated triflates reacted well in the presence of chloride ions. The salt was normally present in a 5-fold excess with respect to the triflate (**2d**). Whereas useful β-regioselectivity was encountered irrespective of the nature of the halide source, chloride ion was found to significantly accelerate the reaction compared to other halides, which appear to quench the reactions giving incomplete conversions.

Table VI. Influence of Bidentate Phosphine Ligands on the Regiochemistry of Arylation of **1** with Phenyl Triflate (**2f**) in the Presence of Lithium Chloride[a].

Ligand	Ligand/Pd[b]	time (h)	Yield of **3f** + **4f** (%)[c]	β/α[d]
$Ph_2P(CH_2)_2PPh_2$ DPPE	2.2	144	56[e]	58/42
$Ph_2P(CH_2)_3PPh_2$ DPPP	2.2	96	41[f,g]	1/99
$Ph_2P(CH_2)_4PPh_2$ DPPB	2.2	120	78	88/12
1,1′-Bis(diphenyl-phosphino)ferrocene DPPF	2.2	42	93	92/8

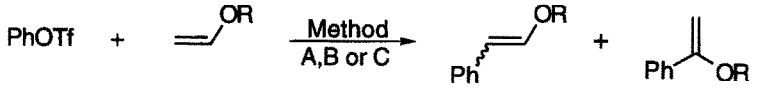
Footnotes: [a] Reactions utilized **1** (2 mmol), **2f** (1 mmol), triethylamine (2 mmol), palladium acetate (0.030 mmol), phosphine ligand (0.066 mmol) and lithium chloride (5 mmol) in 4 ml of DMF at 60 °C. [b] Molar ratio between the phosphine ligand and palladium acetate. [c] Determined by GLC-MS. [d] Determined by GLC-MS and ^{1}H NMR. [e] GLC-MS yield of the β-regioisomers plus the methyl ketone **9f**, obtained after acidic workup. [f] GLC-MS yield of the corresponding methyl ketone **9f**, obtained after acidic workup. [g] Remaining unreacted triflate.

Table VII. Effects of Halide Ions on the Arylation of **1** with 2-Naphthyl Triflate (**2d**)[a].

Additive	Temp (°C)	Ligand	Time (h)	Yield of **3d+4d** (%)[b]	β/α[c]	(*E*)/(*Z*)[c]
NaF	60	-	22[d]	44[e]	99/1	41/59
LiF	60	-	18[d]	55[e]	99/1	41/59
LiCl	60	-	4	84	98/2	10/90
Bu_4NCl[f]	60	-	24	91	96/4	13/87
LiBr	60	-	22[d]	30[e]	98/2	20/80
LiI	60	-	42[d]	8[e]	~80/20[g]	~20/80[g]
None	60	-	42[d]	62[e]	99/1	44/56
LiF	80	PPh_3	5	88	99/1	50/50
LiCl	80	PPh_3	42	95	87/13[h]	74/26
LiBr	80	PPh_3	5	99	87/13[h]	73/27
KBr	80	PPh_3	5	99	95/5[h]	77/23
LiI	80	PPh_3	18[d]	56[e]	74/26[h]	55/45
None	80	PPh_3	5	98	99/1	49/51

Footnotes: [a] Reactions utilized **1** (2 mmol), **2d** (1 mmol), triethylamine (2 mmol), palladium acetate (0.030 mmol) additive salt (5 mmol) and, when present, triphenylphosphine (0.066 mmol) in 4 ml of DMF at 60 °C or 80 °C. [b] Determined by GLC-MS. [c] Determined by GLC-MS and ^{1}H NMR. [d] No further conversion after longer reaction time. [e] Remaining unreacted triflate. [f] Only 2 mmol Bu_4NCl were utilised. [g] Low yield did not allow an accurate determination. [h] The α-arylated isomer gradually hydrolysed to the corresponding methyl-2-naphthylketone under the reaction. β/α was calculated as **3d**/(**4d**+**9d**).

The relatively high preference for formation of the *Z*-product after chloride addition is also notable. Introduction of triphenylphosphine (P/Pd = 2.2) markedly increased the yields and all the reactions proceeded to completion, except reactions in the presence of lithium iodide. Disappointing low β-selectivities were encountered when lithium chloride or lithium bromide was used. The enhanced β/α ratio obtained by replacement of lithium bromide with potassium bromide, we assume reflects the low solubility of KBr.



(16)

2f **1**; R = $CH_2CH_2N(CH_3)_2$ **3f** **4f**

5; R = $CH_2CH_2CH(CH_3)_2$ **6** **7**

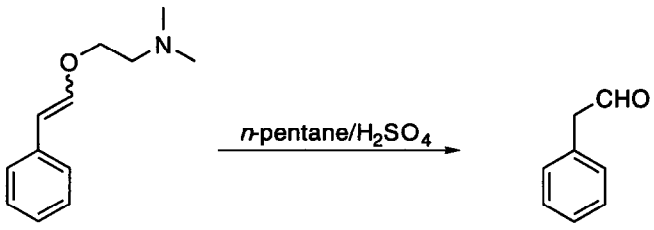
The substrate **1** was originally developed in order to evaluate the potential of chelation in directing the arylation regioselectivity in electron-rich, polarised substrates. However, we have previously observed effects also upon the rate of arylation reactions using a series of vinyl ethers bearing a palladium-chelating functionality.[16] A comparison of the reactivity of **1** and the sterically very similar (3-methyl-1-butoxy)ethene **5** with phenyl triflate (Equation 16) revealed that **1** is a much better substrate than **5** under all conditions employed (Methods A, B and C). For instance, under the simplest conditions (Method A) **5** failed to give arylated products, whereas **1** gave a 44% yield (GLC-MS, β/α=99/1) after 72h. Competitive arylation of **1** and **5** with **2f** (Table VIII) further stressed the difference in substrate reactivity. Irrespective of the conditions, the products derived from **1** (**3f** and **4f**) were strongly dominating those from **5** (**6** and **7**) when the crude reaction mixture was analysed by GLC-MS.

Table VIII. Competitive Arylations of the Substrates **1** and **5** with Phenyl Triflate (**2f**).

		Product distribution					
		Yield (%)[a]		Regioselectivity[b]		Stereoselectivity[b]	
Method[c]	Time (h)	**3f+4f**	**6+7**	**3f/4f**	**6/7**	(*E*)-**3f**/(*Z*)-**3f**	(*E*)-**6**/(*Z*)-**6**
A	6[d]	28[e]	0	99/1		38/62	
B	72	62[e]	11	99/1	≈3/97[f]	47/53	-[f]
C	72	69	23[g]	94/6	61/39	60/40	82/18

Footnotes: [a] Determined by GLC-MS . [b] Determined by GLC-MS and ^{1}H NMR. [c] Reactions utilized **1** (2 mmol), **5** (2 mmol), **2f** (1 mmol), triethylamine (2 mmol) and palladium acetate (0.030 mmol) in 4 ml of DMF. Method A; reactions were carried out at 80 °C in the absence of added phosphine or lithium chloride. Method B; reactions were carried out at 60 °C in the presence of triphenylphosphine (0.066 mmol). Method C; reactions were carried out at 80 °C in the presence of tris(4-methoxyphenyl)phosphine (0.030 mmol) and lithium chloride (5 mmol). [d] No further conversion after longer reaction time. [e] Remaining unreacted triflate. [f] Low yield did not allow an accurate determination. [g] Unidentified by-product was detected.

Finally, we chose to use the parent **3f** to verify the route to 2-phenylethanals (**8**). The hydrolysis of **3f** was easily performed by using an efficient two-phase (*n*-pentane/ H_2SO_4) system.[29] This method effectively diminished any side reactions and gave pure 2-phenylethanal (90%) without chromatography or distillation. The nitrogen functionality in **3f** is crucial for the applicability of the method since the sterically similar enol ether **6** is unaffected by these reaction conditions.

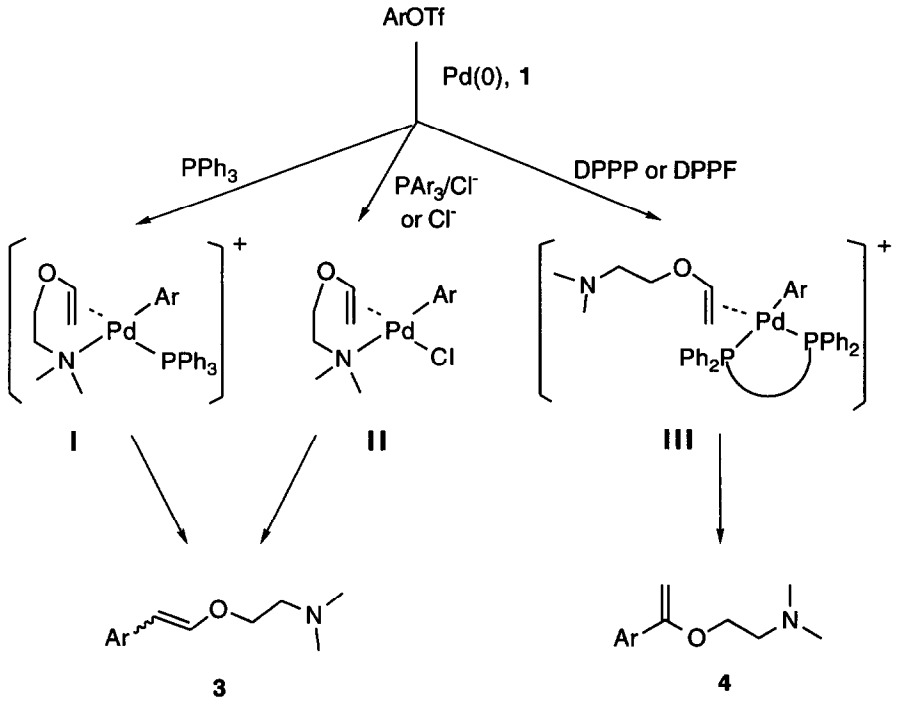


(17)

3f **8**

DISCUSSION

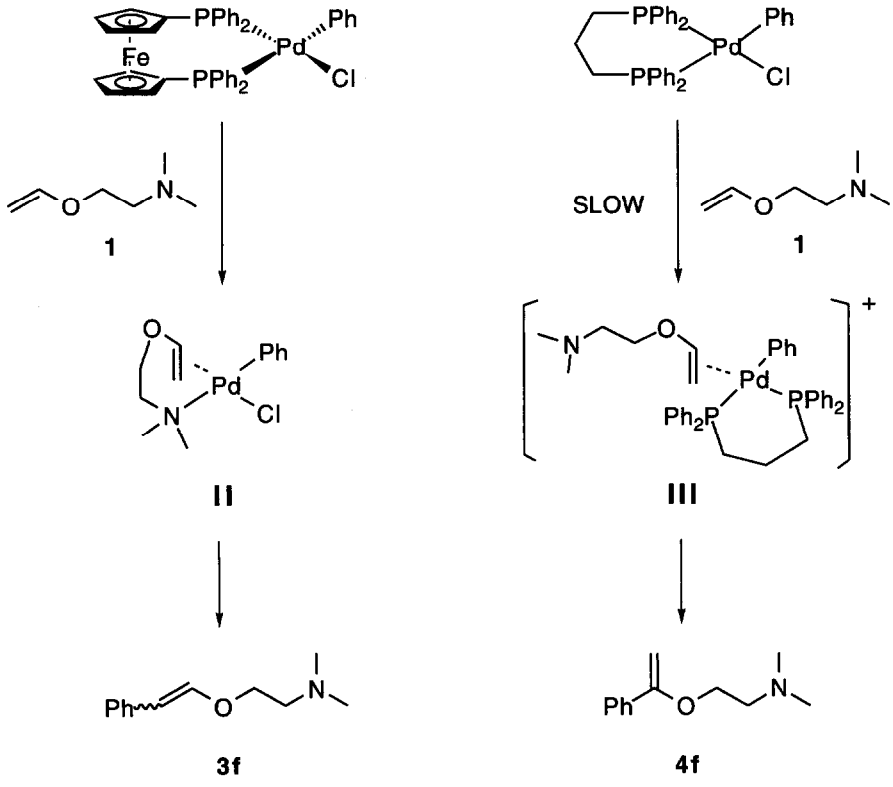
The results presented here demonstrate that aryl triflates are useful in chelation-controlled regioselective arylation reactions involving **1**. Due to the relatively low reactivity of some triflates, phosphine and halide additives have to be introduced in order to achieve good conversions. One exception is illustrated in Table 1. Addition of phosphines to reactions with 1-naphthyl triflate (**2c**) suppressed the conversion rate, most likely as a result of steric interactions with the hydrogen in the 8-position. Chloride ion, in the absence of triphenylphosphine, accelerate the reaction with the activated triflate **2d** relative to experiments in the absence of additives, but bromide and iodide ions impede the conversion (Table VII).



Scheme I

In contrast to these results, the use of chloride ions does not accelerate reactions with non activated triflates, less prone to undergo oxidative addition, suggesting that chloride ions alone do not enhance the rate of oxidative addition. The effect observed with bromide and iodide anions could be due to involvement of a less stable catalytic system, since after addition of triphenylphosphine the yield of the reactions sharply increased. Thus, the combination phosphine-halide (chloride or bromide) provides access to an efficient and stable catalyst facilitating the oxidative addition.

The use of bidentate ligands in order to obtain regiocontrol has been introduced and studied in some detail by Cabri and co-workers, who rationalized the regiochemical outcome dictated, by e.g. DPPP, in terms of a cationic organometallic intermediate.[4,10] A schematic representation of the possible routes for the arylation of **1** is given in Scheme I. As we believe that the substrate **1** reacts by a chelation-controlled procedure, good β-selectivity requires that the substrate can occupy two coordination sites on the metal. It is reasonable to assume that the α-substituted product obtained in the presence of bidentate ligands results from a charge-controlled addition of aryl and palladium in the cationic π-complex **III**. However, our results indicate that the intermediate **I**, which should be formed using Method B, is subject to chelation-directed insertion despite being a cation. Under the conditions of Method A, cationic complexes should also prevail, but having solvent or amine molecules replacing the phosphine in complex **I**.



Scheme II

The combination of phosphine ligand and chloride ions transforms the Pd(0)-complex into an effective catalyst for the olefination of the more sluggish aryl triflates (Method C). This was the only case where the isomers **4** were produced in detectable amounts in the absence of a chelating phosphine. The desired products **3** could still be isolated in useful yields. Arylation of **1** with aryl iodides should involve an iodo complex analogous to **II**, and such reactions produce a similar product distribution.[15] The finding that the chloride additive in Method C caused the formation of minor amounts of **4** would seem to suggest that there is competition between the substrate nitrogen and phosphine or triethylamine in the neutral species **II**, whereas the cationic complex **I** binds the substrate nitrogen more strongly. This suggestion is further supported by the results from the arylation of **1** with 2-naphthyl triflate (**2d**) (Table VII) and phenyl triflate (**2f**) (Table III). Thus, the addition of triphenylphosphine, in the presence of chloride, bromide or iodide ions, exerted, in all cases, a loss of regiocontrol. Further, a high P/Pd ratio disfavoured the regioselectivity in reactions employing both lithium chloride and tris(4-methoxyphenyl)phosphine. In a separate experiment starting from iodobenzene and **1**, we found that thallium (I) addition[10a-b,30] markedly improved β-selectivity, probably by abstracting iodide to form **I** rather than the iodide analogue of **II**.

The selectivity for the formation of products **3** or **4** is determined by a very fine balance between the different species in the Scheme I. A particularly illustrative example of this is the fact that the DPPF-containing catalyst (P/Pd=4.4) gives excellent α-selectivity (**4f**) when LiCl is not added (Table IV) whereas the addition of chloride gives the opposite product **3f** with almost as good selectivity (Table VI and Equation 15). Hence, it appears that the present results may be due to a higher ability of DPPF, compared to DPPP, to dissociate from the neutral oxidative addition complex[27,31], permitting the olefin with its nitrogen ligand to coordinate, and efficiently afford the neutral type **II** complex (Scheme II). Lack of coordination sites in the stable oxidative addition complex[10a-b] explains the slow conversion in the presence of both DPPP and lithium chloride. We speculate that the α-selectivity is a result of chloride-olefin rather than phosphine-olefin exchange.

We have previously shown that chelating substrates (e.g.**1**) can be less reactive than butyl vinyl ether towards iodobenzene.[15] On the other hand, in competitive situations the slower-forming products could sometimes be obtained selectively.[16] We interpret these results by assuming that the catalyst is tied up in relatively stable π- or σ-complexes with a strongly chelating substrate after oxidative addition has occurred. In the present case, where triflates served as the arylating agents and under modified reaction conditions, apparently contradictory results were found. Thus, using either of the Methods, the chelating **1** reacted faster than **5**, and further competitive experiments confirmed that the nitrogen-containing product **3f** could be produced selectively also in the presence of **5**. Unfortunately, the reasons underlying the difference in reactivity are presently unclear. In any event, the higher reactivity of the substrate **1**, when triflates are used as the arylating agents, together with the possibility to perform either α- or β-selective transformations should be useful for producing un-symmetrical diarylated compounds. We are at present evaluating this chemistry for the preparation of e.g. aryl benzyl ketones after cleavage of the enol ether.

CONCLUSION

Chelation-controlled arylation of enol ether **1** with aryl triflates is apparently a useful method for obtaining β-aryl vinyl ethers. Many functional groups are tolerated on the aryl triflate, although the more electron-rich aryl triflates couple only with an appropriate choice of ligands and salts. Moreover, the coupling of aryl triflates with coordinating **1** provides a ready transformation of a phenol, *via* its triflate, into the free arylacetaldehyde in high yield. In fact, in the preparation of arylacetaldehydes from **1**, the amino function is helpful not only in controlling regioselectivity, but also in facilitating both the purification and cleavage of the aryl enol ethers by simple extraction procedures. Our results have further established the practicability of controlling the regioselectivity in both directions through the addition of bidentate phosphine ligands or lithium chloride.

EXPERIMENTAL PART

General information. ^{1}H-NMR spectra were recorded with TMS as an internal standard at 270 MHz on a Jeol EX 270 spectrometer. Low resolution electron-impact MS spectra were measured with a Hewlett-Packard mass spectrometer HP5971A MSD connected to a gas chromatograph HP GC5890 Series 2, equipped with a HP-1 (25 m x 0.2 mm) column. The column temperature was 50-290 °C (gradient, 10 °C / min). Isomers were assumed to have the same response factor. Column chromatography was performed on silica gel 60 (0.040-0.063 mm, Merck) or on aluminium oxide 90 (0.063-0.200 mm, Merck). Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. All arylation reactions were run in heavy-walled, oven-dried, thin-necked Pyrex tubes, sealed with a screw-cap fitted with a Teflon gasket. Samples were periodically removed, under nitrogen, partitioned between diethyl ether and 0.1 M NaOH, and analyzed by GLC-MS. Determination of the product distribution and the (*E*)/(*Z*) ratio was made by GLC-MS, in combination with ^{1}H-NMR. The α-arylated isomers (**4**) gradually decomposed and were, after acidic workup, isolated as the corresponding methyl ketones (**9**).

Materials. Palladium(II) acetate was obtained from Merck. Triethylamine was distilled from potassium hydroxide prior to use. The enol ethers **1** and **5** were prepared as described elsewhere.[15,16] Tri-2-furyl-phosphine was prepared following a literature procedure.[32] 2,6-Diethylphenol was generously supplied by AB Astra. DMF was stored over activated 4Å molecular sieves and degassed with nitrogen before use. Compounds **6** and **7** were prepared according to our own procedure[16] and purified by column chromatography (silica gel, *n*-pentane / diethyl ether, 9/1). Aryl triflates were prepared from the corresponding phenols by a standard procedure using 2,4,6-trimethylpyridine as base[33] or, in the case of **2j**, 2,6-di-*t*-butylpyridine.[34] Triflates **2a**-**2g** and **2i** are known compounds, and their structures were determined by comparison of their spectroscopic data with the reported values.[10a,35,36] The triflates **2h** and **2j** exhibited spectroscopic data as summarised below. All other reagents were commercially obtained and used as received.

4-tert-Butylphenyl trifluoromethanesulfonate (**2h**) was obtained in 90% yield as a colourless oil. Kugelrohr distillation (~0.3 mm Hg, oven temperature ~80 °C). Anal. Calcd. for $C_{11}H_{13}F_3O_3S$ (282.3): C, 46.8; H, 4.6. Found: C, 46.8; H, 4.8. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.47-7.16 (m, 4H, aryl), 1.32 (s, 9H). MS [IP 70 eV; *m/z* (% rel. int.)]: 282 (15, M), 267 (100), 175 (10), 134 (7).

2,6-Diethylphenyl trifluoromethanesulfonate (**2j**) was obtained in 72% yield as a pale yellow oil. Kugelrohr distillation (~0.5 mm Hg, oven temperature ~90 °C). Anal. Calcd. for $C_{11}H_{13}F_3O_3S$ (282.3): C, 46.8; H, 4.6. Found: C, 47.0; H, 4.5. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.29-7.15 (m, 3H, aryl), 2.78 (q, 4H, J=7 Hz), 1.25 (t, 6H, J=7 Hz). MS [IP 70 eV; *m/z* (% rel. int.)]: 282 (52, M), 149 (100), 121 (36).

General procedure for preparative β-arylation reactions (Table I).

Method A. To a stirred solution of the aryl triflate (5.0 mmol) in DMF (20 ml) under a nitrogen atmosphere each of the reactants were added in the following order: palladium acetate (0.0337 g, 0.15 mmol), triethylamine (1.01 g, 10 mmol) and **1** (1.15 g, 10 mmol). The reaction mixture was stirred magnetically and heated to 80 °C for 6-72 h. After cooling, the black mixture was diluted with *n*-pentane (100 ml) or diethyl ether (**3e**), transferred to a separatory funnel and washed with water (2x50 ml). Additional extraction of the aqueous phases was performed with *n*-pentane (50 ml) or diethyl ether (**3e**). The combined organic portions were then treated 5 times with 50 ml of 0.1 M HCl (effecting selective decomposition of possible α-isomer, Method C). The aqueous extracts were combined and poured into a flask containing excess NaOH (1.0 M) and pentane (100 ml) or diethyl ether (100 ml). After 10 min of stirring, the phases were separated and the aqueous layer extracted with additional *n*-pentane (100 ml) or, in the case of **3e**, diethyl ether (100 ml). The combined organic phases were washed with brine (50 ml), dried (K_2CO_3) and concentrated by evaporation.

This workup procedure afforded products of satisfactory purity (GLC-MS analysis indicated a purity of >94% for all β-arylated products), but samples for elemental analysis were further purified by bulb-to-bulb distillation.

Method B. Palladium acetate (0.0337 g, 0.15 mmol) and triphenylphosphine (0.0866 g, 0.33 mmol) were dissolved in DMF (20 ml) under a stream of nitrogen. To the orange solution were added in the following order: aryl triflate (5.0 mmol), triethylamine (1.01 g, 10 mmol) and **1** (1.15 g, 10 mmol). The reaction mixture was heated to 60 °C with stirring, whereby it slowly darkened. After the completion the reaction mixture was allowed to cool and was purified as described in Method A.

Method C. A stock solution containing palladium acetate (0.337 g, 1.5 mmol) and tris(4-methoxyphenyl)-phosphine (0.529 g, 1.5 mmol) in 200 ml DMF was prepared under nitrogen. The arylating agent (5.0 mmol) was charged in the reaction vessel and 20 ml of the stock solution was added. The remaining starting agents, lithium chloride (1,06 g, 25 mmol), triethylamine (1.01 g, 10 mmol) and **1** (1.15 g, 10 mmol) were introduced and the vessel was capped and heated at 80 °C with stirring in an oil bath. After 18-120 h, GLC-MS analysis showed that the starting aryl triflate had been consumed. The β-product was purified according to Method A. The products **3a**, **3c**, **3f** and **3i** were described by us in an earlier publication[15].The remaining β-arylation products (as *(E)*/*(Z)* mixtures) exhibited spectral and analytical properties as summarized below.

N,N-Dimethyl-2-[2-(4-cyanophenyl)ethenyloxy]ethanamine (**3b**): from Method B; yellow oil; *(E)*/*(Z)* mixture. Kugelrohr distillation (~0.5 mm Hg, oven temperature ~170 °C). Anal. Calcd. for $C_{13}H_{16}N_2O$ (216.3): C, 72.2; H, 7.5; N, 13.0. Found: C, 72.0; H, 7.6; N, 12.9. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.65-7.25 (m, 4H, aryl), 7.16 (d, 0.4H, J=13 Hz) *E*, 6.36 (d, 0.6H, J=7 Hz) *Z*, 5.83 (d, 0.4H, J=13 Hz) *E*, 5.24 (d, 0.6H, J=7 Hz) *Z*, 4.08 (t, 1.2H, J=6 Hz) *Z*, 3.96 (t, 0.8H, J=6 Hz) *E*, 2.69-2.60 (dt, 2H), 2.32 (s, 6H). MS [IP 70 eV; *m/z* (% rel. int.)]: 216 (6, M), 116 (2), 72 (8), 58 (100).

N,N-Dimethyl-2-[2-(2-naphthyl)ethenyloxy]ethanamine (**3d**): from Method A; yellow oil; *(E)*/*(Z)* mixture. Kugelrohr distillation (~0.5 mm Hg, oven temperature ~170 °C). Anal. Calcd. for $C_{16}H_{19}NO$ (241.3): C, 79.6; H, 7.9. Found: C, 79.6; H, 8.2. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.02-7.23 (m, 7H, aryl), 7.17 (d, 0.4H, J=13 Hz) *E*, 6.28 (d, 0.6H, J=7 Hz) *Z*, 6.00 (d, 0.4H, J=13 Hz) *E*, 5.38 (d, 0.6H, J=7 Hz) *Z*, 4.07 (t, 1.2H, J=6 Hz) *Z*, 3.96 (t, 0.8H, J=6 Hz) *E*, 2.70-2.60 (dt, 2H), 2.34 (s, 3.6H) *Z*, 2.32 (s, 2.4H) *E*. MS [IP 70 eV; *m/z* (% rel. int.)]: 241 (9, M), 152 (5), 141 (5), 72 (59), 58 (100).

N,N-Dimethyl-2-[2-(4-acetylphenyl)ethenyloxy]ethanamine (**3e**): from Method B; colourless oil; *(E)*/*(Z)* mixture. The material obtained by Kugelrohr distillation (~0.3 mm Hg, oven temperature ~160 °C) contained impurities and was further purified by chromatography (aluminium oxide, eluting with 2% Et_3N in *n*-pentane / ethyl acetate, 7/3). Anal. Calcd. for $C_{14}H_{19}NO_2$ (233.3): C, 72.1; H, 8.2. Found: C, 72.0; H, 8.4. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.90-7.26 (m, 4H, aryl), 7.18 (d, 0.5H, J=13 Hz) *E*, 6.34 (d, 0.5H, J=7 Hz) *Z*, 5.86 (d, 0.5H, J=13 Hz) *E*, 5.27 (d, 0.5H, J=7 Hz) *Z*, 4.07 (t, 1H, J=6 Hz) *Z*, 3.96 (t, 1H, J=5 Hz) *E*, 2.70-2.63 (dt, 2H), 2.57 (s, 1.5H) *Z*, 2.56 (s, 1.5H), 2.33 (s, 3H) *Z*, 2.32 (s, 3H)*E*. MS [IP 70 eV; *m/z* (% rel. int.)]: 233 (6, M), 145 (1), 102 (2), 72 (20), 58 (100).

N,N-Dimethyl-2-[2-(4-chlorophenyl)ethenyloxy]ethanamine (**3g**): from Method B; yellow oil; *(E)*/*(Z)* mixture. Kugelrohr distillation (~0.5 mm Hg, oven temperature ~180 °C). Anal. Calcd. for $C_{12}H_{16}ClNO$ (225.7): C, 63.9; H, 7.1; N, 6.2. Found: C, 64.1; H, 7.5; N, 6.4. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.69-7.10 (m, 4H, aryl), 7.00 (d, 0.4H, J=13 Hz) *E*, 6.22 (d, 0.6H, J=7 Hz) *Z*, 5.79 (d, 0.4H, J=13 Hz) *E*, 5.18 (d, 0.6H, J=7 Hz) *Z*, 4.03 (t, 1.2H, J=6 Hz) *Z*, 3.92 (t, 0.8H, J=5 Hz) *E*, 2.69-2.59 (dt, 2H), 2.31 (s, 3.6H) *Z*, 2.31 (s, 2.4H) *E*. MS [IP 70 eV; *m/z* (% rel. int.)]: 227 (1), 225 (5, M), 125 (2), 101 (3), 72 (29), 58 (100).

N,N-Dimethyl-2-[2-(4-tert-butylphenyl)ethenyloxy]ethanamine (**3h**): from Method B, yellow oil; (*E*)/(*Z*) mixture. Kugelrohr distillation (~0.5 mm Hg, oven temperature ~200 °C). Anal. Calcd. for $C_{16}H_{25}NO$ (247.4): C, 77.7; H, 10.2; N, 5.7. Found: C, 77.4; H, 10.5; N, 5.8. ^1H NMR (270 MHz, $CDCl_3$): δ 7.53-7.13 (m, 4H, aryl), 7.01 (d, 0.5H, J=13 Hz) *E*, 6.17 (d, 0.5H, J=7 Hz) *Z*, 5.83 (d, 0.5H, J=13 Hz) *E*, 5.21 (d, 0.5H, J=7 Hz) *Z*, 4.01 (t, 1H, J=6 Hz) *Z*, 3.91 (t, 1H, J=6 Hz) *E*, 2.70-2.61 (dt, 2H), 2.32 (s, 3H) *Z*, 2.31 (s, 3H) *E*, 1.30 (s, 4.5H) *Z*, 1.30 (s, 4.5H) *E*. MS [IP 70 eV; *m/z* (% rel. int.)]: 247 (9, M), 159 (1), 145 (2), 72 (73), 58 (100).

General procedure for screening reactions (Table II-VII).
Phosphine or arsine ligand, when present, (0.030-0.120 mmol), halide salt, when present, (2.0-5.0 mmol), aryl triflate (1.0 mmol), triethylamine (0.204 g, 2.0 mmol) and enol ether (**1**, 2.0 mmol) were sequentially added under nitrogen to a catalyst solution of palladium acetate (0.0067 g, 0.030 mmol) and 2,3-dimethylnaphthalene or naphthalene (internal standard, 0.050 g) in DMF (4 ml). After heating at the appropriate temperature for the times indicated (see tables for details) in a closed tube, samples were taken up in diethyl ether and washed with 0.1 M NaOH (Table II-IV and VI-VII) or treated with 1 M HCl (Table IV-VI). The product distribution and the yield of the reaction were determined by GLC-MS analysis. Aryl ketones **9a-9i** are commercially available and **9j** is a known compound.[37,38]

*Procedure for preparative α-arylation reactions (**4a, 4h, 4j**, Table V) and isolation of the corresponding aryl methyl ketone (**9a, 9h, 9j**).*
A solution of palladium acetate (0.0337 g, 0.15 mmol) and DPPP (0.136 g, 0.33 mmol) in DMF (20 ml) was stirred under nitrogen. Aryl triflate (5.0 mmol), triethylamine (1.01 g, 10 mmol) and **1** (1.15 g, 10 mmol) were added and the tube was flushed with nitrogen, sealed and heated at 60 °C for 14-120 h. The mixture was partitioned between *n*-pentane (100 ml) and water (2x50 ml), and the organic layer was separated and treated with HCl (1 M, 50 ml) for 30 min with stirring. The organic phase was washed with water (2x50 ml), dried (K_2CO_3) and concentrated in vacuo. The crude **9a** was further purified by flash chromatography (silica gel; *n*-pentane / ethyl acetate, gradient (9/1-7/3 by volume). Bulb-to-bulb distillation (~10 mm Hg, oven temperature ~140 °C) of the crude **9j** afforded pure product as a colourless oil.

*Competitive arylation reactions of the enol ethers **1** and **5** with phenyl triflate (**2f**) (Table VIII).*
Palladium acetate (0.0067 g, 0.030 mmol), 2,3-dimethylnaphthalene (internal standard, 0.050 g) and, if present, phosphine ligand (0.030-0.066 mmol) were dissolved in DMF (4 ml) under nitrogen. Lithium chloride, when present, (0.212 g, 5.0 mmol), phenyl triflate (1.0 mmol), triethylamine (0.204 g, 2.0 mmol), **1** (0.231 g, 2.0 mmol) and finally **5** (0.228 g, 2.0 mmol) were added and the tube was immersed in a bath at 60 °C or 80 °C. The reactions were monitored by GLC-MS (samples removed from the mixture and partitioned between diethyl ether and NaOH (0.1 M). Determination of the product distribution was made on small samples of the crude material, removed prior to workup. GLC-MS analyses were performed on a 25 m x 0.32 mm CP Wax 51 column, in addition to the standard HP-1 column.

*Hydrolysis of **3f** to 2-phenylethanal (**8**) (Equation 17).*
A solution of **3f** (0.383 g, 2.0 mmol) in *n*-pentane (16 ml) was added to the sulphuric acid (4 ml conc. H_2SO_4/ 16 ml water) under stirring at room temperature. After the addition, stirring was continued for 2 h before the pentane layer was separated. Additional extraction of the aqueous phase was performed with diethyl ether (25 ml). The combined organic portions were washed with brine and dried over anhydrous sodium sulphate. Removal of the solvent at aspirator pressure afforded 0.216 g (90%) of pure **8**.

Reaction of 4-Nitrophenyl triflate (**2a**) *with* **1** *without palladium-catalyst.*
Into a Pyrex tube charged with 5 ml of DMF were added 0.271 g (1.0 mmol) of **2a**, 0.231 g (2.0 mmol) of **1** and 0.204 g (2.0 mmol) of triethylamine. The solution was heated with stirring at 80 °C for 24 h. GLC-MS analysis of the reaction mixture showed that the starting **2a** had been consumed and indicated the presence of *N*-Methyl-*N*-(4-nitrophenyl)-2-(ethenyloxy)ethanamine. The reaction also furnished minor amounts of di-4-nitrophenyl ether as deduced from ^{1}H NMR, ^{13}C NMR, GLC-MS, FTIR and m.p.[39] The cool reaction mixture was worked up by dilution with 25 ml of 0.1 M HCl and subsequent extraction with two 25 ml diethyl ether. The combined organic phases were washed with brine, dried (K_2CO_3) and concentrated by evaporation. Column chromatography on silica gel (*n*-pentane / ethyl acetate, 5/1 by volume) afforded 0.06 g *N*-Methyl-*N*-(4-nitrophenyl)-2-(ethenyloxy)ethanamine as a yellow solid (15% yield). Mp 78-80 °C. Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222.2): C, 59.4; H, 6.4; N, 12.6. Found: C, 59.2; H, 6.5; N, 12.2. ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.03 (d, 2H, J=9 Hz), 6.57 (d, 2H, J=10 Hz), 6.37 (dd, 1H, J=7, 14 Hz), 4.11 (dd, 1H, J=2, 14 Hz), 3.97 (dd, 1H, J=2, 7 Hz), 3.82 (t, 2H, J=5 Hz), 3.67 (t, 2H, J=5 Hz), 3.06 (s, 3H). MS [IP 70 eV; *m/z* (% rel. int.)]: 222 (17, M), 165 (100), 119 (39).

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