Direct Synthesis of Protected Arylacetaldehydes by Palladium-Tetraphosphine-Catalyzed Arylation of Ethyleneglycol Vinylether

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Abstract: Through the use of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-*tetrakis*(diphenylphosphinomethyl) cyclopentane as a catalyst, a range of aryl bromides undergo Heck reaction with ethyleneglycol vinylether to give regioselectively protected arylacetaldehydes in good yields. The β-arylation products were obtained in the range 93–98% selectivity with electron-poor aryl bromides. Furthermore, this catalyst can be used at low loading, even for reactions of sterically hindered aryl bromides. The arylvinyl ethers intermediates undergo subsequent ketalization to give the corresponding 2-benzyl-1,3-dioxolane derivatives.

Key words: palladium, catalysis, tetraphosphine, Heck reaction, aryl bromides, ethyleneglycol vinylether, arylacetaldehydes

Palladium-catalyzed functionalization of aromatic halides has become an important method in preparative organic chemistry.[1] Nevertheless, arylation of electron-rich olefins such as enol ethers is often limited by poor α:β regioselectivity.[2–6] High α-regioselective arylations in the presence of *n*-butylvinylether have been reported by Cabri et al. and Hallberg et al. in the presence of $Pd(OAc)_2$/dppp.[7–10] In some procedures, TlOAc was added in order to improve the regioselectivity of the reaction. The reaction performed in ionic liquids as solvent also led selectively to the α-arylation.[11] On the other hand, poly(ethylene glycol) used as solvent with $Pd(OAc)_2$ as catalyst led selectively to the β-arylated products.[12] It has been demonstrated that the regioselectivity of the addition of organopalladium intermediates can be influenced by coordinating groups adjacent to the substrate double bond.[13–16] For example, Hallberg et al. have described that the nitrogen containing vinyl ethers [2-(dimethylamino)ethoxy]-ethene in the presence of palladium acetate led to regioselective β-arylation of several aryl halides.[13,15] On the other hand, in the presence of ethylene glycol vinylether with $Pd(OAc)_2$/dppp as catalyst they obtained selectively the α-arylations to give aryl vinyl ethers, which undergo subsequent ketalization to form selectively the isomer **e** in Scheme 1.[17] Surprisingly, to our knowledge, the selective β-arylation in the presence of ethylene glycol vinylether has never been described.

In order to obtain stable and efficient palladium catalysts, we have prepared the new tetraphosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-*tetrakis*(diphenylphosphinomethyl)cyclopentane or Tedicyp[18] (Scheme 1) in which four diphenylphosphino groups are stereospecifically bound to the same face of a cyclopentane ring. We have already reported the results obtained in allylic substitution,[18] for Suzuki cross-coupling,[19] and for Sonogashira alkynylation[20] using Tedicyp as the ligand. We have also reported several results obtained for Heck vinylation reaction.[21] We had observed that with *n*-butylvinyl ether in the presence of the tetraphosphine Tedicyp associated to $[Pd(C_3H_5)Cl]_2$, high reaction rates but moderate to good regioselectivities in favour of β-arylation could be obtained,[21c] but in many cases these selectivities were not high enough to provide a useful process for the preparation of protected arylacetaldehydes. In order to improve the selectivity of the reaction in favor of the β-addition with our catalyst, we have decided to investigate arylation reactions with enol ethers containing a coordinating substituent in order to achieve higher regiochemical control. Here, we report our studies involving an alcohol-containing substrate derived from ethyl vinyl ether: ethylene glycol vinylether.

For this study, based on previous results,[21c] DMF was chosen as the solvent and potassium carbonate as the base. The reactions were performed at 130 °C under argon in the presence of a ratio 1:2 of $[Pd(C_3H_5)Cl]_2$–Tedicyp as catalyst.

First, we investigated the Heck reaction of electron-poor and electron-rich aryl bromides with ethyleneglycol vinylether in the presence of the system Pd–Tedicyp catalyst (Scheme 1, Table 1). The results presented in Table 1 disclose a strong influence of the substituents on the aryl bromides on the regioselectivity of the addition and on the reaction rate. We obtained high efficiency and good regioselectivities in favor of β-arylation with electron-poor aryl bromides such as 4-bromoacetophenone, 4-bromobenzonitrile, 4-nitrobromobenzene, or 4-trifluoromethylbromobenzene. The β-selectivities observed were in the range 93–98% (entries 1–8). Even electron-poor *ortho*-substituted aryl bromides gave satisfactory results (entries 6–8). Moreover, most of these reactions were performed with high ratios substrates:catalyst (up to 10 000). On the other hand, the reaction performed with the electron-rich aryl bromides: 4-*t*-butylbromobenzene or 2-methylbromobenzene led to lower selectivities. With these substrates, larger amounts of α-arylated products were obtained (entries 13 and 14). Bromobenzene or iodobenzene also led to mixtures of α- and β-arylated products

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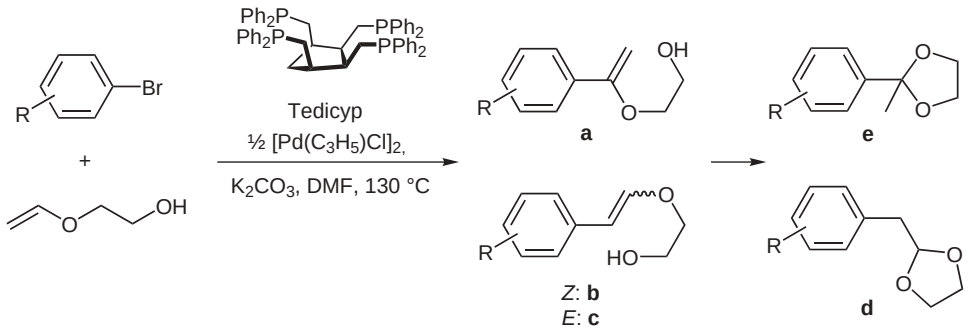

Scheme 1

Table 1 Tedicyp–Palladium-Catalyzed Selective Synthesis of Protected Arylacetaldehydes from Ethyleneglycol Vinylether and Aryl Halides[a,23,24]

Entry	Aryl halide	Ratio substrate:catalyst	Selectivity **a**:**b**:**c**:**d**:**e** (%)	Ratio **b**+**c**+**d**:**a**+**e**	Isomer **d** product number	Yield of isomer **d** (%)
1	4-Bromoacetophenone	10 000	0:0:0:93:7	93:7	**1d**	87
2	4-Bromobenzaldehyde	10 000	0:0:0:97:3	97:3	**2d**	91
3	4-Bromobenzonitrile	10 000	0:0:0:98:2	98:2	**3d**	92
4	4-Nitrobromobenzene	1 000	0:0:0:98:2	98:2	**4d**	87
5	4-Trifluoromethylbromobenzene	10 000	0:0:0:94:6	94:6	**5d**	90
6	2-Bromobenzaldehyde	250	0:0:0:96:4	96:4	**6d**	77
7	2-Bromobenzonitrile	1 000	3:0:0:97:0	97:3	**7d**	91
8	2-Trifluoromethylbromobenzene	10 000	0:0:0:94:6	94:6	**8d**	88
9	3,4-Difluorobromobenzene	250	0:0:0:85:15	85:15	**9d**	79
10	4-Fluorobromobenzene	250	0:0:0:57:43	57:43	**10d**	52
11	Bromobenzene	100	0:13:41:13:33	67:33	**11d**	89[b]
12	Iodobenzene	100	0:10:11:57:22	78:22	**11d**	52
13	4-*t*-Butylbromobenzene	250	0:10:29:27:34	66:34	**12d**	87[b]
14	2-Methylbromobenzene	100	17:6:15:62:0	83:17	**13d**	57
15	1-Bromonaphthalene	1 000	0:0:0:78:22	78:22	**14d**	74
16	9-Bromoanthracene	1 000	0:0:0:90:10	90:10	**15d**	79
17	3-Bromopyridine	1 000	12:0:0:88:0	88:12	**16d**	83
18	4-Bromopyridine	1 000	3:0:0:97:0	97:3	**17d**	88
19	3-Bromoquinoline	10 000	10:0:0:90:0	90:10	**18d**	85
20	4-Bromoisoquinoline	1 000	12:0:0:88:0	88:12	**19d**	81
21	5-Bromopyrimidine	1 000	0:0:0:100:0	100:0	**20d**	76

[a] Conditions: catalyst: $[Pd(C_3H_5)Cl]_2$–Tedicyp 1:2, aryl halide (1 mmol), ethyleneglycol vinylether (2 mmol), K_2CO_3 (2 mmol), DMF, 130 °C, 20 h, under argon, isolated yields of isomer **d**, ratio of isomers determined by GC and ^1H NMR of the crude mixtures.
[b] Yield of the mixture containing all the isomers **b**–**e**.

(entries 11 and 12) indicating that the lower regioselectivities observed with electron-rich aryl bromides does not comes from a slower oxidative addition of the aryl halide. The sterically hindered substrates 1-bromonaphthalene and 9-bromoanthracene gave β-arylated products in 78 and 90% selectivities, respectively, indicating that the regioselectivity of the addition is partially controlled by steric factors (entries 15 and 16).

Next, we studied the reaction in the presence of heteroaryl bromides (entries 17–21). Pyridines or quinolines are π-electron deficient, so we could expect similar results with bromopyridines or bromoquinolines than with electron-poor aryl bromides. With 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline selectivities of 88%, 90% and 88% in favor of β-arylation were obtained, respectively. The highest selectivities with heteroaromatic substrates were observed with 4-bromopyridine and 5-bromopyrimidine (98% and 100%, respectively).

The intramolecular cyclization of the arylalkenes **a**, **b** and **c** (Scheme 1) was generally observed to give the corresponding 2-benzyl-1,3-dioxolane **d** and 2-methyl-2-phenyl-1,3-dioxolane **e** derivatives. This ketal formation is not palladium-catalyzed, but arise through internal nucleophilic attack of the hydroxyl group.[22] Faster cyclization reactions were observed with electron-deficient substrates. For example, when 4-*t*-butylbromobenzene was used, mixtures of cyclized and uncyclized products were obtained. On the other hand, in the presence of 4-bromoacetophenone or 3,5-*bis*(trifluoromethyl)bromobenzene only ketal products were detected.

In order to determine if an ether function instead of an alcohol on the vinylether would have an effect on the control of the regioselectivity of the addition, we performed the reaction in the presence of ethyleneglycol *n*-butylvinyl diether and *n*-butylvinylether (ratio substrat–catalyst: 1000, see Scheme 2). We observed that very similar mixtures of isomers were obtained and in both case large amounts of α-arylated products were formed (24% and 25%, respectively). In the presence of ethyleneglycol vinylether the formation of only 6% of α-arylated product had been observed (Table 1, entry 5).

Finally, we compared our catalytic system with the system PPh_3 (4 equiv) and $[Pd(C_3H_5)Cl]_2$ (1 equiv) for this reaction with 9-bromoanthracene. In the presence of 0.4% catalyst, the ratio of products **b**+**c**+**d**:**a**+**e** was 72:28. Moreover, compound **15d** was isolated in a low yield (21%). With this catalyst, a very important debromation of 9-bromoanthracene was observed and the major product of the reaction was anthracene.

In summary, we have established that the Tedicyp–palladium system provides a convenient catalyst for the synthesis of protected arylacetaldehyde derivatives by coupling of aryl bromides with ethyleneglycol vinylether followed by intramolecular ketalization. The electronic control of the regioselectivity of the addition encountered with *n*-butylvinylether appears to be partially suppressed by an adjacent alcohol function. Anchoring the enol to the metal by an alcohol function probably imposes a conformational change in the structure of the (aryl)Pd(enol) intermediate and stabilizes a neutral Pd-complex favoring the formation of the β-arylated products.[1c] The best selectivities in favor of β-arylations were observed with electron-poor aryl bromides. With bromobenzene or electron-rich aryl bromides mixtures or regioisomers were observed. In all cases, only traces (<1%) of homocoupling products were observed with this catalyst. Ethyleneglycol vinylether is commercially available, moreover, the reaction can be performed with as little as 0.01% catalyst with several substrates, so this catalyst appears to be among the most active and stable ones reported so far for this reaction. Due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

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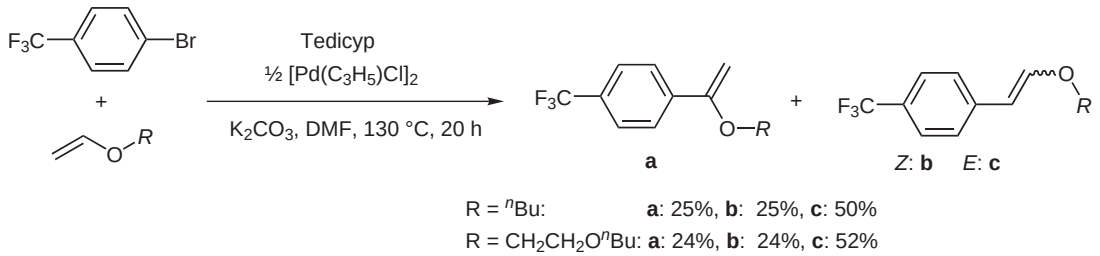

Scheme 2

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(23) **As a Typical Experiment: Synthesis of 2-(4-Acetylbenzyl)-1,3-dioxolane(1d).**
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), K_2CO_3 (0.276 g, 2 mmol) and ethylene glycol vinylether (0.176 g, 2 mmol) at 130 °C during 20 h in anhyd DMF (5 mL) in the presence of the Tedicyp-palladium complex (0.1 μmol) under argon affords the corresponding coupling product after extraction with Et_2O, separation, drying ($MgSO_4$), evaporation and filtration on silica gel (Et_2O–/pentane 1:4) in 87% (0.179 g) isolated yield. White solid, mp 55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.1 Hz, 2 H, Ar), 7.36 (d, *J* = 8.1 Hz, 2 H, Ar), 5.08 (t, *J* = 5.1 Hz, 1 H, CH_2CH), 3.95–3.80 (m, 4 H, CH_2CH_2), 3.02 (d, *J* = 5.1 Hz, 2 H, CH_2CH), 2.56 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 141.7, 135.6, 129.9, 128.3, 103.9, 65.0, 40.6, 26.5. MS: *m*/*z* calcd for $C_{12}H_{14}O_3$: 206; found: 206 (19%). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62; H, 6.63. Before purification, traces of 2-methyl-2-(4-acetylphenyl)-1,3-dioxolane(**1e**) were also observed: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2 H, Ar), 7.55 (d, *J* = 8.3 Hz, 2 H, Ar), 4.03 (m, 2 H, CH_2CH_2), 3.75 (m, 2 H, CH_2CH_2), 2.57 (s, 3 H, Me), 1.62 (s, 3 H, Me).

(24) All new compounds gave satisfactory ^{1}H NMR, ^{13}C NMR and elemental analysis data.