J. Org. Chem. 1988, *53*, 4257–4263

Palladium-Catalyzed Aroylation of Alkyl Vinyl Ethers. An Entry to Monoprotected 1-Aryl-1,3-dicarbonyl Equivalents

Carl-Magnus Andersson and Anders Hallberg*

Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Received January 11, 1988

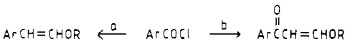
Reaction of aromatic and heteroaromatic acid chlorides with alkyl vinyl ethers in the presence of a palladium catalyst and an amine base gives the *E*-β-aroylated vinyl ethers **3** in moderate to good yield. The reaction proceeds under mild conditions and tolerates a variety of substituents, although strongly electron withdrawing groups give inferior yields as a result of a competitive decarbonylative arylation process. The common intermediate is an acylpalladium chloride complex, resulting from oxidative addition of Pd(0) to the acid chloride. The mechanism of the reaction is discussed in terms of this intermediate.

Introduction

A plethora of transition metal catalyzed coupling reactions of acid chlorides with organometallics has been developed during the past decade.[1] In particular, the palladium-catalyzed reactions often proceed efficiently and selectively, and useful applications including the coupling of aroyl chlorides with organic derivatives of mercury,[2] tin,[3] zinc,[4] and silicon[5] have been demonstrated. In contrast to this, only very few examples of the catalytic insertion of olefins into acylpalladium complexes, related to the very general Heck arylation reaction,[6] have appeared.[7]

In a study of palladium-catalyzed decarbonylation reactions, Tsuji and Ohno observed the formation of minor amounts of 1,5-diphenyl-1-penten-3-one on applying the reaction to phenylpropionyl chloride.[8] The formation of this compound was rationalized as a palladium-catalyzed acylation. More recently, Chiusoli's group has briefly reported the reaction of methyl acrylate with benzoyl chloride in the presence of a palladium or nickel catalyst, to give methyl benzoylacrylate.[9]

In connection with our studies directed toward the synthetic utilization of palladium-catalyzed substitution on heteroatom-substituted olefins such as enol ethers,[10] we recently reported the transformation of benzoyl chloride derivatives into the corresponding arylacetaldehyde enol ethers[11] (reaction a in eq 1) via a decarbonylative vinylic substitution reaction.[12] In that reaction, minor amounts of the aroylated vinyl ethers, at least formally derived from a palladium-catalyzed acylation reaction, were sometimes observed (reaction b in eq 1).

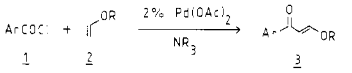


$$\mathrm{ArCH{=}CHOR} \xleftarrow{a} \mathrm{ArCOCl} \xrightarrow{b} \mathrm{Ar\overset{\overset{O}{\|}}{C}CH{=}CHOR} \qquad (1)$$

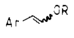
Herein, we report an extended study of palladium-catalyzed reactions of aroyl chlorides with olefins.[13] Successful aroylation of simple vinyl ethers can be accomplished in good yields and under mild conditions. The reaction constitutes a new entry to monoprotected 1-aryl-1,3-dicarbonyl equivalents.

Results

Aromatic acid chlorides **1** reacted with alkyl vinyl ethers **2** to furnish 1-aryl-3-alkoxy-2-propen-1-ones **3** in good yields (Table I). The reactions were performed by using catalytic amounts of a palladium reagent and in the presence of a slight excess of an amine base (eq 2).



(2)



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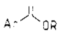

5

The major byproducts were (*E*)- and (*Z*)-2-alkoxyethenyl aromatics **4** and 1-alkoxyethenyl aromatics **5**, produced as a result of carbon monoxide extrusion from the intermediate palladium complex (vide infra). The reaction of benzoyl chloride (**1a**) with butyl vinyl ether (**2a**) was used as a model system in a study of some general features of the reaction.

General Conditions. Initial experiments utilized *N*-ethylmorpholine as the base, since it performed well in the analogous arylation reactions.[11,12] A comparison of a series of amine bases[14] revealed that triethylamine in the present

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[1] (a) For a review, see: Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551–564. (b) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *291*, 129.

[2] (a) Larock, R. C.; Bernhardt, J. C. *J. Org. Chem.* **1978**, *43*, 710. (b) Takagi, K.; Okamoto, T.; Sukakibara, Y.; Ohno, A.; Oka, S.; Hayami, N. *Chem. Lett.* **1975**, 951.

[3] (a) For a review, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767. (c) Soderquist, J. A.; Leong, W. W.-H. *Tetrahedron Lett.* **1983**, *24*, 2361. (d) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129; (e) **1983**, *105*, 669. (f) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. (g) Milstein, D.; Stille, J. K. *Ibid.* **1979**, *44*, 1613. (h) Verlhac, J.-B.; Chanson, E.; Jousseaume, B.; Quintard, J.-P. *Tetrahedron Lett.* **1985**, *26*, 6075.

[4] (a) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. (b) Negishi, E.; Bagneri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Ibid.* **1983**, *24*, 5181.

[5] Yamamoto, K.; Hayashi, A.; Suzuki, S.; Tsuji, J. *Organometallics* **1987**, *6*, 974.

[6] For reviews, see: (a) Heck, R. F. *Org. React.* (*N.Y.*) **1982**, *27*, 345–390. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: London, 1985; pp 276–290.

[7] Examples of insertion processes in stoichiometric reactions have appeared; see: (a) Otsuka, S.; Nakamura, A.; Yoshida, T.; Naruto, M.; Ataka, K. *J. Am. Chem. Soc.* **1973**, *95*, 3180. (b) Heck, R. F. *Ibid.* **1971**, *93*, 6896; (c) **1969**, *91*, 6707. The carboalkoxylation of olefins by palladium catalysis might also involve the addition of acylpalladium species; see: (d) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, 1987; pp 635, 391.

[8] Tsuji, J.; Ohno, K. *J. Am. Chem. Soc.* **1968**, *90*, 94.

[9] (a) Chiusoli, G.-P. *Pure Appl. Chem.* **1980**, *52*, 635. (b) Biavati, A.; Chiusoli, G.-P.; Costa, M.; Terengi, G. *Transition Met. Chem.* (*Weinheim, Ger.*) **1979**, *4*, 398.

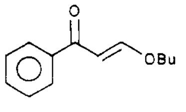
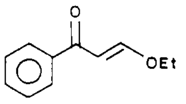
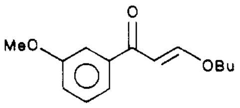
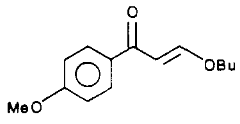
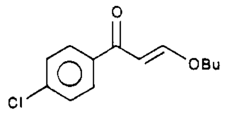
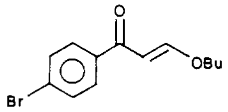
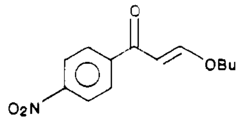
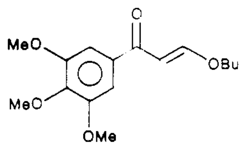
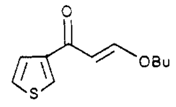
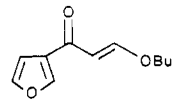
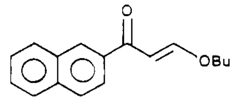
[10] (a) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529. (b) Hallberg, A.; Westfelt, L.; Andersson, C.-M. *Synth. Commun.* **1985**, *15*, 1131. (c) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414.

[11] Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235.

[12] (a) Blaser, H.-U.; Spencer, A. *J. Organomet. Chem.* **1982**, *233*, 267. (b) Spencer, A. *Ibid.* **1982**, *240*, 209; (c) **1983**, *247*, 117; (d) **1984**, *265*, 323.

[13] Part of this work was reported in a preliminary communication: Andersson, C.-M.; Hallberg, A. *Tetrahedron Lett.* **1987**, *28*, 4215.

Table I. 1-Aryl-3-alkoxy-2-propen-1-ones Prepared by Palladium-Catalyzed Aroylation of Vinyl Ethers

compd	yield,[a] %	^{1}H NMR:[b] δ	MS[c]	elemental anal. calcd	elemental anal. found	eluent[d]
 **3a**	69	7.86–7.92 (m, 2 H), 7.77 (d, 1 H), 7.40–7.56 (m, 3 H), 6.35 (d, 1 H), 3.99 (t, 2 H)	204 (1), 187 (0.4), 175 (7), 161 (17), 147 (47), 133 (10)	C, 76.44 H, 7.90	76.4 7.90	pentane/EtOAc 4/1
 **3b**	54	7.86–7.92 (m, 2 H), 7.76 (d, 1 H), 7.40–7.56 (m, 3 H), 6.35 (d, 1 H), 4.06 (q, 2 H), 1.40 (t, 3 H)	176 (4), 161 (7), 147 (14), 133 (23), 120 (2), 105 (37), 71 (100)	C, 74.98 H, 6.86	74.6 6.85	pentane/EtOAc 4/1
 **3c**	62	7.75 (d, 1 H), 7.42–7.47 (m, 2 H), 7.30–7.37 (m, 1 H), 7.03–7.08 (m, 1 H), 6.33 (d, 1 H), 3.84 (s, 3 H), 3.97 (t, 2 H)	234 (19), 217 (1), 205 (4), 191 (9), 177 (27), 163 (19)	C, 71.77 H, 7.74	71.5 7.78	pentane/Et$_2$O 2/1
 **3d**	77	7.87–7.93 (m, 2 H), 7.74 (d, 1 H), 6.84–7.00 (m, 2 H), 6.35 (d, 1 H), 3.98 (t, 2 H)		C, 71.77 H, 7.74	70.9 7.63	pentane/Et$_2$O 2/1
 **3e**	40	7.81–7.86 (m, 2 H), 7.77 (d, 1 H), 7.38–7.45 (m, 2 H), 6.31 (d, 1 H), 4.00 (t, 2 H)		C, 65.41 H, 6.33	65.2 6.30	pentane/Et$_2$O 3/1
 **3f**	56	7.70–7.78 (m, 3 H), 7.52–7.58 (m, 2 H), 6.28 (d, 1 H), 3.97 (t, 2 H)	282 (0.2),[e] 253 (0.8), 239 (2), 225 (3), 211 (1), 198 (0.3), 183 (4)	C, 55.14 H, 5.34	55.2 5.32	pentane/Et$_2$O 3/1
 **3g**	12	8.25–8.35 (m, 2 H), 7.98–8.04 (m, 2 H), 7.81 (d, 1 H), 6.32 (d, 1 H), 4.03 (t, 2 H)	249 (0.1), 220 (2), 206 (2), 194 (2), 192 (1), 176 (3)	C, 62.64 H, 6.06 O, 25.67	62.6 6.14 25.5	pentane/Et$_2$O 5/1
 **3h**	57	7.75 (d, 1 H), 7.15 (s, 2 H), 6.33 (d, 1 H), 4.01 (t, 2 H), 3.92 (s, 6 H), 3.90 (s, 3 H)		C, 65.29 H, 7.53 O, 27.18	64.8 7.48 27.2	pentane/Et$_2$O 1/1
 **3i**	66	7.98 (dd, 1 H, *J* = 3, 1 Hz), 7.75 (d, 1 H), 7.55 (dd, 1 H, *J* = 5, 1 Hz), 7.31 (dd, 1 H, *J* = 5, 3 Hz), 6.23 (d, 1 H), 3.98 (t, 2 H)	210 (14), 181 (3), 167 (19), 153 (9) 139 (6), 126 (8)	C, 62.83 H, 6.71	63.0 6.67	pentane/Et$_2$O 3/1
 **3j**	40	7.98 (dd, 1 H, *J* = 1, 1.5 Hz), 7.74 (d, 1 H), 7.44 (dd, 1 H, *J* = 2, 1.5 Hz), 6.80 (dd, 1 H, *J* = 2, 1 Hz), 6.01 (d, 1 H), 3.97 (t, 2 H)	194 (4), 165 (8), 151 (4), 137 (3), 121 (5), 110 (11), 96 (25), 95 (23)	C, 68.02 H, 7.26	67.7 7.22	pentane/Et$_2$O 4/1
 **3k**	55	7.4–8.0 (m, 8 H), 6.51 (d, 1 H), 4.00 (t, 2 H)	254 (24), 237 (1), 225 (4), 211 (13), 197 (30), 183 (24)	C, 80.28 H, 7.13	78.9 7.14	pentane/Et$_2$O 3/1

[a] Isolated yields. [b] In CDCl$_3$. In all the butoxy compounds, the three terminal groups of protons (OCH$_2$C*H*$_2$C*H*$_2$C*H*$_3$) appeared at the same shifts: δ 1.73 (m, 2 H), 1.45 (m, 2 H), 0.96 (t, 3 H). [c] Relative intensities are given in parentheses. The basic peak was *m/e* = 41, unless stated. [d] Solvent mixture used for flash chromatography (see Experimental Section). [e] Bromine isotope peaks excluded.

Table II. Benzoylation of Butyl Vinyl Ether in Various Solvents at 50 °C[a]

solvent	rctn time and yield,[b] % 12 h	24 h
toluene	76	74
acetonitrile	40	55
tetrahydrofuran	28	36
butyl vinyl ether	86	70
1,2-diethoxyethane	65	65
triethylamine	58	52
methylene chloride	30	47

[a] The reactions utilized benzoyl chloride (10 mmol), triethylamine (12 mmol), butyl vinyl ether (20 mmol), and palladium acetate (0.2 mmol). Five milliliters of the indicated solvent was added. [b] GLC yields.

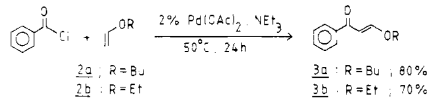
Table III. Catalysts for the Benzoylation of Butyl Vinyl Ether in Toluene at 50 °C[a]

catalyst	yield,[b] %
$Pd(OAc)_2$	69
$PdCl_2$	68
$Pd(PhCN)_2Cl_2$	87
Pd/C	52
none	0

[a] The reactions utilized benzoyl chloride (10 mmol), butyl vinyl ether (20 mmol), triethylamine (12 mmol), and the palladium catalyst indicated (0.2 mmol) in 5 mL of toluene. The reaction time was 24 h. [b] GLC yields.

case could be used without affecting the yield, and this base is now generally used.

The reaction was best performed at 50–70 °C, with 50 °C preferred. The reaction of benzoyl chloride with vinyl ether under such conditions (eq 3) typically produced a 70–80% yield of the β-aroyl enol ethers 3.



(3)

Higher reaction temperatures gave extensive decarbonylation to produce primarily the arylated compounds 4 and 5. Although the reaction also took place at room temperature, it was too slow for preparative purposes. For instance, the reaction of benzoyl chloride with ethyl vinyl ether (**2b**) gave a 70% yield of **3b** after 24 h at 70 °C, whereas the reaction at room temperature needed 6 days to reach the same conversion.

Polar as well as nonpolar solvents resulted in good conversion, although the best yields were obtained by using either toluene or an excess of butyl vinyl ether as the solvent (Table II). In most cases, a turbid reaction solution was encountered as a result of acylammonium halide formation. In reactions employing aroyl chlorides with low solubility, methylene chloride sometimes proved advantageous.

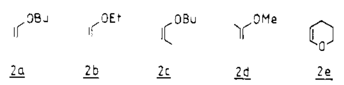
Catalyst Precursors. The choice of catalyst precursor was not critical, and 1–2% of a simple palladium salt was sufficient (Table III). Interestingly, palladium on charcoal also promoted the reaction, but was somewhat less efficient. When the reaction was performed in toluene, $(PhCN)_2PdCl_2$ was superior due to its better solubility in this solvent, but in reactions employing an excess of the olefin as solvent, $Pd(OAc)_2$ was usually satisfactory, and these conditions were used for preparative experiments.

Table IV. Effect of Added Triphenylphosphine on the Benzoylation of Ethyl Vinyl Ether in Acetonitrile at 50 °C[a]

catalyst	mol % PPh_3 added[b]	yield,[c] %
$Pd(OAc)_2$	0	44
$Pd(OAc)_2$	1	9
$Pd(OAc)_2$	2	trace
$Pd(PPh_3)_4$	0	0

[a] Benzoyl chloride (10 mmol), ethyl vinyl ether (20 mmol), N-ethylmorpholine (12 mmol), and the palladium catalyst (1 mol %) were heated in acetonitrile (10 mL) for 24 h. [b] Based on benzoyl chloride. [c] GLC yields.

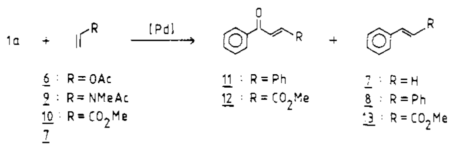
Chart I



No reaction was observed in the absence of palladium catalyst.

Phosphines were shown to significantly influence the rate as well as the regioselectivity in palladium-catalyzed arylations of enol ethers.[10a] In the present aroylation, triphenylphosphine was found to efficiently inhibit the reaction.[15] As can be seen from Table IV, even 1% of triphenylphosphine decreased the yield 4-fold, and 2% inhibited the reaction totally. Tetrakis(triphenylphosphine)palladium did not function as a catalyst in the reaction, even at 100 °C.

Alkenes. As depicted in eq 4, a series of alkenes were subjected to the standard reaction conditions (50 °C, toluene, triethylamine, 2% $Pd(OAc)_2$). Under these conditions, butyl vinyl ether gave a 76% yield of benzoylated **3a** and a 17% total yield of the phenylated products (**4a**, Ar = Ph, R = Bu; and **5a**, Ar = Ph, R = Bu). Surprisingly, disappointing results were encountered with all olefins except vinyl ethers under the standard conditions.



(4)

Vinyl acetate (**6**) resulted exclusively in products derived from cleavage of the carbon–oxygen bond and decarbonylation, producing styrene (**7**) and stilbene (**8**) in approximately 10% yield. Elimination of palladium and acetate anion has been reported previously in similar systems.[11,16] N-Vinyl-N-methylacetamide (**9**) provided only a trace of benzoylated product, as deduced by GLC–MS analysis of the reaction mixture. Although both styrene (**7**) and methyl acrylate (**10**) reacted to give low yields of products, comparable amounts of phenylated and benzoylated products resulted. Thus, styrene gave stilbene (**8**, 13%) and chalcone (**11**, 9%), and methyl acrylate gave methyl benzoylacrylate (**12**, 12%) together with methyl cinnamate (**13**, 5%).

Some alkyl-substituted enol ethers were next studied as substrates (Chart I). It was found that none of the alkyl-substituted compounds **2c–e** were as efficient as **2a** or **2b**.

Only **2c** reacted, to give the phenylated isomers in about 10% yield, and a trace of the benzoylated product was detected by GLC–MS. The possibility to force the reaction

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[14] The following amines were assessed: tri-n-butylamine, triethylamine, benzyldimethylamine,[12] and ethyldiisopropylamine. Inorganic bases were unsuccessful.

[15] Spencer's group also reported inhibition by phosphines in the related decarbonylative arylation.[12a] Our result is in contrast to that of Chiusoli's group,[9b] where benzoylation was accomplished by using a phosphine-ligated catalyst. For a discussion of the effect of phosphines on the rate of oxidative addition, see ref 3f.

[16] Arai, I.; Daves, G. D., Jr. J. Heterocycl. Chem. 1978, 15, 351.

at elevated temperatures was limited, since the decarbonylation then became predominant. It is recognized that substituents on the double bond decrease olefin reactivity in Heck arylations.[6]

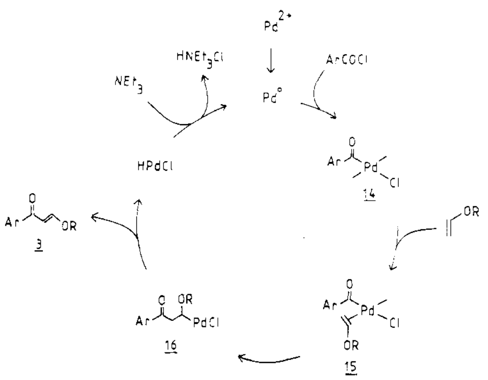
Aroyl Chlorides. In contrast to the limitations in the use of olefins other than simple alkyl vinyl ethers, the expected tolerance to substituents in the aroyl chloride was confirmed. The results from preparative experiments employing a variety of substituted aromatic and heteroaromatic acid chlorides are depicted in Table I. The yields refer to isolated compounds. Purification was generally effected by flash chromatography, but large-scale preparations followed by distillation were also feasible (see Experimental Section). Reasonable generality was observed with meta- and para-substituted aroyl chlorides. Reaction at the acid chloride function was possible without interference by bromo or chloro substituents. While electron-donating substituents favored the reaction, electron-withdrawing groups gave lower yields. The latter was primarily a result of facile carbon monoxide extrusion, but also to some extent to side reactions with the base. A severe limitation is that ortho-substituted aroyl chlorides cannot be used. All the tested ortho-substituted chlorides (*o*-toluoyl chloride, *o*-acetoxybenzoyl chloride, *o*-chlorobenzoyl chloride, and *o*-nitrobenzoyl chloride) gave only traces of the desired **3**, accompanied by a comparatively large amount of decarbonylation products **4** and **5**.[5] Furthermore, 2-thiophenecarbonyl chloride, as opposed to the 3-analogue (Table I), gave a low yield accompanied by tar formation, and 2-furancarbonyl chloride and the hydrochloride of 3-pyridinecarbonyl chloride furnished complex product mixtures. Benzoyl bromide gave extensive tar formation.

Discussion

The apparent limitations of the present reaction pose several interesting questions regarding the mechanism. This is especially the case with the unexpected reluctance of olefins recognized to be particularly efficient in the Heck reaction to undergo substitution. A straightforward mechanistic rationale that accounts for all experimental findings is difficult to present.

Action of the Catalyst. The operation of a palladium-catalyzed Friedel–Crafts reaction,[17] with Pd(II) acting as a Lewis acid, is in our opinion less likely in this reaction and was ruled out as a consequence of several experimental findings. Hence, (a) the reaction is subject to palladium(0) catalysis (e.g., palladium on charcoal, vide supra) (The facility of the oxidative addition of acid chloride to palladium(0) under the conditions is demonstrated by the competitive formation of decarbonylation products.); (b) alkyl-substituted enol ethers (e.g., **2d**), expected to show high reactivity in a Lewis acid catalyzed process, failed to react; (c) 4-methoxybenzoyl chloride gives a much better yield than 4-nitrobenzoyl chloride, a more potent electrophile (Table I).

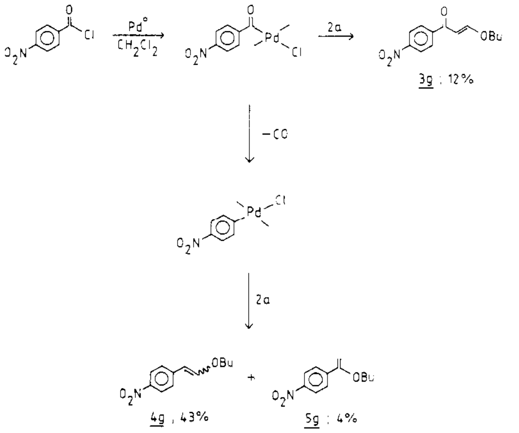
Scheme I



A mechanistic rationale for the formation of aroylated product involving the oxidative addition of Pd(0) to form an acylpalladium intermediate **14**, following the pathway outlined for Heck-type reactions, is thence most probable (Scheme I). A pathway completely analogous to the Heck arylation reaction would involve a (presumably concerted) collapse of an intermediate π-complex **15** to produce the (σ-alkyl)palladium species **16**. Elimination of hydridopalladium chloride provides the benzoylated product **3**. This mechanism was put forward to account for the analogous stoichiometric reaction of carbomethoxypalladium salts with alkenes.[7c]

Regiochemistry. The regiochemical outcome in reactions of arylpalladium halides with unsymmetrical olefins is primarily governed by steric factors.[6] In cases where the double bond of the olefin is highly polarized and electron-rich, e.g., in enol ethers, electronic factors play an important role and regioisomeric mixtures often result (vide infra). Although preference for arylation at either the terminal or oxygen-bearing carbon of the olefin can be induced by proper selection of reaction conditions and starting materials,[10a] regio- and stereoisomeric mixtures are invariably produced.

Interestingly, throughout this study, *exclusively* the *E*-β-substituted product was observed, regardless of the conditions. Hence, it seems as if the addition of acylpalladium halide over the olefinic bond is much more selective than the corresponding addition of arylpalladium halide. The reaction of 4-nitrobenzoyl chloride with butyl vinyl ether in methylene chloride provided a comparatively large amount of the arylated products (vide infra) and is particularly illustrative. This reaction was chosen for a detailed study (eq 5).



(5)

Thus, while only the *E*-β-aroylated compound **3g** was isolated, in the same pot, all possible isomers of the corresponding arylated compounds were formed. The ratio of **4g** ($E/Z \approx 1/1$) to **5g** was 10:1. Such a difference in selectivity is unlikely to stem from steric effects.[18]

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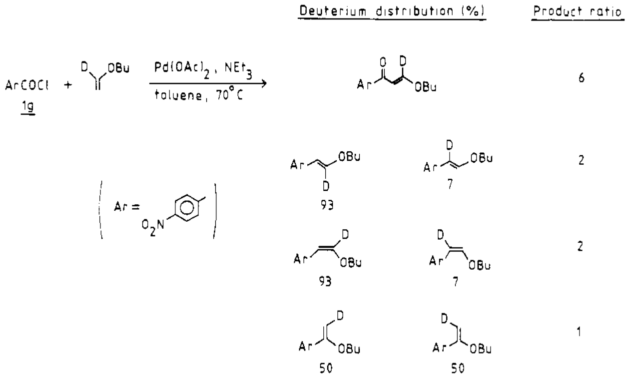
[17] Trihaloacetylation of enol ethers and related compounds has been reported recently. (a) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1986**, 1013. (b) Hojo, M.; Masuda, R.; Kokurio, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499. (c) For related acylation of enamines, see: Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* **1982**, *23*, 1201.

[18] It should be noted that 4-nitrophenylation results in particularly high β-selectivity.[10a,b] Significantly, 4-methoxybenzoyl chloride also gave exclusive β-aroylation in the present study, thus even more sharply contrasting the corresponding phenylation reaction in which the α-substituted product was obtained as the major product from 4-iodoanisole.[10c]

Scheme II

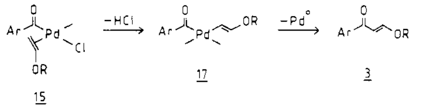


The same reaction was performed by starting from butyl α-deuteriovinyl ether, and the deuterium distribution in the product mixture was roughly estimated by ^{2}H NMR and GLC analyses. Scrambling of the deuterium was observed in the arylated products, but not in the aroylated compound (Scheme II). Only minor deuterium loss was encountered. Furthermore, much more scrambling was found in the α-arylated compound ($\approx$100%) than in the two β-isomers ($\approx$7%).

This trend in scrambling ratios could indicate that the rates of readdition of palladium hydride/deuteride to the respective products are significantly different.[7c] Alternatively, as is outlined below, two different modes of formation of, on one hand, the α-arylated and, on the other hand, the β-arylated and the aroylated compounds might be considered.

On the basis of the findings that the arylation of electron-rich olefins generally proceeds to give large amounts of the internally substituted products as a consequence of electronic control, we find the abnormally high β-selectivity encountered in the aroylation process difficult to rationalize. Thus, the collapse of the π-complex **15** ought to be directed by a strong interaction between the electron-deficient palladium atom and the carbon with the highest electron density in the enol ether.[10a,19] By electronic considerations, the opposite regioisomer should be expected to form, at least in minor amounts. Furthermore, involvement of a Heck-type mechanism should permit facile substitution even on the electron-poor olefins tested. In fact, such olefins are generally preferred as substrates in the Heck arylation.[6]

It has been suggested that in the transmetalation between acylpalladium chloride and, e.g., vinylstannanes, the palladium atom acts as the electrophile in an electrophilic substitution reaction,[3d] and thus it is tempting to assume that a similar type of reaction also operates in this case, with the vinyl ether acting as the nucleophile (eq 6). This rationale could explain the abnormally high selectivity for β-substitution encountered in this aroylation.[20] Such a process must not necessarily leave a hydridopalladium species coordinated to the product double bond and, consequently, be accompanied by deuterium scrambling.



(6)

The sluggish reaction observed with electron-poor alkenes supports this assumption, but the low reactivity of alkyl-substituted enol ethers is not accounted for. Precedence for reductive elimination of acyl and alkenyl ligands from palladium(II) complexes, such as **17**, is available from coupling reactions.[3]

Aroylation vs Arylation. The reaction gave the best yields starting from aroyl chlorides with electron-releasing substituents, whereas the electron-poor aroyl chlorides resulted in lower yields (compare 4-methoxybenzoyl chloride and 4-nitrobenzoyl chloride, Table I). The main reason for this was that the arylated products **4** and **5** were formed instead. Similar observations were reported in a recent paper,[5] describing the preparation of aroyltrimethylsilanes by a related procedure.[21,22] Another feature of the reaction is that the presence of vinyl ether rather than less electron rich alkenes appears to suppress decarbonylation[11,12] (vide supra). This is presumably a result of blocking of coordination sites by the vinyl ether. Vinyl ethers have been suggested to be particularly good ligands to divalent palladium.[23]

Conclusion. Aroyl chlorides as precursors to organopalladium intermediates are useful starting materials that provide access to (a) β-arylvinyl ethers in a regioselective decarbonylation/arylation process and, on minor modifications of the reaction conditions, (b) β-aroylvinyl ethers in a remarkably regio- and stereoselective aroylation reaction. The latter masked 1-aryl-1,3-dicarbonyl equivalents have potential interest, e.g., in heterocycle synthesis. However, the preparative utility of the aroylation is restricted to unsubstituted vinyl ethers and fairly electron rich aroyl chlorides, which are apparently less prone to decarbonylate. It seems that the reaction pathway is related to that of the Heck reaction, although the mechanistic details remain obscure.

Experimental Section

Instrumentation. ^{1}H and ^{2}H NMR spectra were recorded on a Varian XL-300 spectrometer in deuteriochloroform and chloroform, respectively. Chemical shifts are given relative to internal tetramethylsilane or tetramethylsilane-d_{12}. Elemental analyses were obtained from the Microanalytical Laboratory at the University of Lund. Mass spectra were obtained on a Finnigan 4021 (Data System Incos 2100) gas chromatograph–mass spectrometer, operating at 70 eV. Gas chromatographic analyses were performed on a Varian 3700 instrument, equipped with a 2.5 m × 2 mm glass column and a flame-ionization detector. The stationary phase was 5% OV 17 on Chromosorb W. A Varian 4270 integrator was used for the determination of peak areas, relative to an internal standard. Silica gel 60 (E. Merck, 0.040–0.0064 mm) was used for flash chromatography, essentially performed as described by Still and co-workers.[24] Melting points are uncorrected.

Materials. Acid chlorides were prepared by refluxing commercially available acids in thionyl chloride for a period of 3–5 h, in the presence of DMF as a catalyst. Purification was achieved by distillation or recrystallization prior to use. 3-Thiophenecarboxylic acid was prepared from 3-bromothiophene by a literature procedure.[25]

The enol ethers, with the exception of butyl (*Z*)-1-propenyl ether (**2c**), were commercially obtained and used as received. Compound **2c** was prepared from allyl butyl ether by rearrangement with base.[26] Butyl α-deuteriovinyl ether, with a deuterium content of 35%, was prepared through deprotonation

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(19) Lee, T. D.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 399.

(20) We have earlier considered a similar mechanism to account for high β-selectivity in certain arylation reactions of enol ethers.[10a]

(21) Decarbonylation of aromatic acid halides normally requires temperatures above 200 °C; see: Verbicky, J. W.; Dellacoletta, B. A.; Williams, L. *Tetrahedron Lett.* **1982**, *23*, 371.

(22) For a discussion of transition metal catalyzed decarbonylations, see ref 7d, pp 768–775.

(23) Wakatsuki, Y.; Nozakura, S.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3426.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(25) Moses, P.; Gronowitz, S. *Ark. Kemi* **1961**, *18*, 119.

(26) Prosser, T. J. *J. Am. Chem. Soc.* **1961**, *83*, 1701.

of butyl vinyl ether with *t*-BuLi,[27] followed by quenching with deuterium oxide, and distillation. The ^2H NMR peak appeared at 6.47 ppm (dd, $J = 2.2, 1.2$ Hz). Amine bases and solvents were distilled prior to use.

Palladium salts were purchased from Johnson-Matthey Chemicals and were used as received. Palladium on charcoal (10%) was obtained from Riedel-de-Haën. Tetrakis(triphenylphosphine)palladium[28] and dichlorobis(benzonitrile)palladium(II)[29] were prepared by the standard procedures.

Screening Reactions. A. Benzoylation of Butyl Vinyl Ether in Various Solvents (Table II). Triethylamine (12 mmol, 1.20 g), butyl vinyl ether (20 mmol, 2.00 g), and naphthalene (internal standard, 0.50 g) were charged in a thin-necked Pyrex tube. To this solution was added palladium acetate (0.2 mmol, 0.045 g) dissolved in 5 mL of the appropriate solvent (Table II). Benzoyl chloride (10 mmol, 1.41 g) was then added, and the tube was closed with a screw cap fitted with a Teflon gasket. The contents were thoroughly mixed, and the tube was immersed in an oil bath, maintained at 50 °C. GLC analysis of the reaction mixture was performed on samples taken up in diethyl ether and washed with a small quantity of water. The response factor of **3a** relative to naphthalene was determined by using the distilled product, obtained from a large-scale preparation.

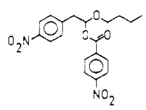
B. Comparison of Catalysts (Table III). These reactions were performed by following the procedure given in A. The catalyst indicated in Table III (2%) was used. After reaction at 50 °C in 5 mL of toluene for 24 h, the yield was determined as above.

C. Effect of Triphenylphosphine (Table IV). Ethyl vinyl ether (20 mmol, 1.45 g), *N*-ethylmorpholine (12 mmol, 1.38 g), and naphthalene (internal standard, 0.50 g) were charged in a Pyrex tube (see A). Tetrakis(triphenylphosphine)palladium (0.1 mmol, 0.115 g) or palladium acetate (0.1 mmol, 0.022 g) together with triphenylphosphine (0–0.2 mmol) was stirred in 10 mL of acetonitrile until a homogeneous solution was obtained. This solution was added to the reaction tube, followed by benzoyl chloride (10 mmol, 1.41 g), and the tube was capped. After heating at 50 °C for 24 h, the reaction mixture was partitioned between diethyl ether and water and analyzed by GLC.

D. Reaction of Benzoyl Chloride with Olefins 6, 7, 9, and 10. The reactions were conducted according to the procedure given in A, with olefin **6**, **7**, **9**, or **10** replacing **2a**. Toluene (5 mL) was used as the solvent. The reaction was performed at 50 °C for 12 h. Identification of the products **7**, **8**, and **11–13** was made by GLC–MS and by comparison of the GLC retention times with those of authentic samples. The yields were estimated by GLC, using the standard addition technique.

E. Attempted Aroylation of Enol Ethers 2c–e. Palladium acetate (0.2 mmol, 0.045 g) was dissolved in a mixture of triethylamine (12 mmol, 1.20 g) and 5 mL of the enol ether (**2c**, **2d**, or **2e**) in the reaction vessel (see A). Benzoyl chloride (10 mmol, 1.41 g) was introduced, and the mixture was heated to 50 °C for 19 h. In the reaction starting from **2c**, GLC–MS analysis proved the presence of a 10% yield of the isomeric phenylpropenyl butyl ethers.[10a]

F. Reaction of 4-Nitrobenzoyl Chloride with Butyl Vinyl Ether. A sealed tube (see A) containing 4-nitrobenzoyl chloride (10 mmol, 1.8 g), triethylamine (12 mmol, 1.2 g), butyl vinyl ether (15 mmol, 1.5 g), and palladium acetate (0.2 mmol, 0.044 g) in 20 mL of methylene chloride was heated to 65 °C. After 15 h, the crude mixture was diluted with 100 mL of diethyl ether and filtered. The ethereal solution was washed with two 50-mL portions of 1 M NaOH, followed by 25 mL of water. The combined aqueous phases were extracted with 50 mL of diethyl ether and acidified to give 0.15 g (9%) of recovered 4-nitrobenzoic acid. The combined ethereal phases were dried ($MgSO_4$) and concentrated at aspirator pressure to give 1.9 g of a dark oil, which was subjected to flash chromatography (pentane/diethyl ether, 5/1). Early fractions contained the decarbonylation products **4g** (0.95 g, 43%) and **5g** (0.09 g, 4%). Further elution gave 0.6 g of yellow crystals, which on trituration with diethyl ether gave **3g** (0.30 g, 12%) and 0.25 g of a pale yellow crystalline compound (mp 119–20 °C), which was assigned the structure I, probably formed during aqueous workup: ^1H NMR δ 8.28–8.33 (m,2 H), 8.14–8.22 (m, 4 H), 7.42–7.50 (m, 2 H), 6.24 (t, 1 H), 3.74 (dt, 1 H), 3.51 (dt, 1 H), 3.25 (d, 2 H), 1.55 (m, 2 H), 1.30 (m, 2 H), 0.86 (t, 3 H). Anal. Calcd for $C_{19}H_{20}N_2O_7$: C, 58.75; H, 5.19; N, 7.21. Found: C, 59.43; H, 5.22; N, 7.23.



I

On GLC analysis, I eliminated 4-nitrobenzoic acid to give an apparent chromatogram of (*E*)- and (*Z*)-**4g**. HPLC analysis on a chiral column (triacetylcellulose) afforded two peaks of equal intensity, demonstrating the presence of two enantiomers.

G. Reaction of 4-Nitrobenzoyl Chloride with Butyl α-Deuteriovinyl Ether. Dichlorobis(benzonitrile)palladium (15.3 mg, 0.04 mmol) was dissolved in a mixture of triethylamine (2.4 mmol, 0.24 g) and 3 mL of toluene. To this solution was added a mixture of butyl α-deuteriovinyl ether (4 mmol, 0.40 g; 35% deuterium by ^2H NMR) and 4-nitrobenzoyl chloride (2 mmol, 0.28 g). After heating to 70 °C for 7 h in a sealed tube (see A), the mixture was diluted with 25 mL of pentane. After filtration and concentration under reduced pressure, ^2H NMR analysis was performed on the crude material. The results are summarized in Scheme II. Assignment of the deuterium signals was based on the chemical shifts observed in the vinylic region in the corresponding ^1H NMR spectra (**3g**, δ 7.78, 6.35; **4g**, δ 4.81, 4.40; *trans*-**5g**, δ 7.19, 5.84; *cis*-**5g**, δ 6.40, 5.26). Product ratios obtained by ^2H NMR integrals were fully confirmed by GLC analysis. Also, the deuterium distributions calculated from the spectrum of the crude material were confirmed by spectra recorded on the pure compounds, isolated as described in F.

Preparative Reactions. General Procedure for the Preparation of 1-Aryl-3-alkoxy-2-propen-1-ones (Table I). Spectral and analytical data for the compounds synthesized (**3a–k**) are compiled in Table I. IR spectra were in accordance with the given structures. The preparation of 1-phenyl-3-butoxy-2-propen-1-one (**3a**) is representative. To a mixture of butyl vinyl ether (40 mmol, 4.0 g) and triethylamine (12 mmol, 1.2 g) in a Pyrex tube was added palladium acetate (0.1 mmol, 0.02 g). The mixture was stirred until a homogeneous yellow solution was obtained. Benzoyl chloride (10 mmol, 1.4 g) was added and the tube closed with a screw cap fitted with a Teflon gasket. The tube was heated to 60 °C in an oil bath. Within 30 min, the color changed from yellow to red. After 18 h, the dark slurry was poured into 50 mL of diethyl ether, and the triethylamine hydrochloride was filtered off. After removal of the solvent and excess butyl vinyl ether under reduced pressure (bath temperature 60 °C), the oily residue was subjected to flash chromatography. There was obtained 1.4 g (69%) of **3a** as a pale-yellow oil. The product gave a semicarbazone with mp 235 °C (lit.[30] 238 °C).

Large-Scale Preparation of 1-Phenyl-3-butoxy-2-propen-1-one (3a). To a mixture of butyl vinyl ether (100 mL) and triethylamine (0.3 mol, 30 g) in a 250-mL round-bottomed flask was added palladium acetate (0.002 mol, 0.45 g), and the mixture was stirred until it was homogeneous. Benzoyl chloride (0.2 mol, 28.1 g) was added, and the flask was closed with a stopper. After heating to 60–65 °C for 18 h, the dark-brown, cake-like residue was transferred to a beaker containing 300 mL of diethyl ether. Filtration and concentration gave 46 g of a red-brown oil, which was distilled under reduced pressure. A forerun (bp 60–70 °C (0.03 mmHg)) contained the phenylated products **4a** and **5a** (3.9 g, 11%). The title compound **3a** was obtained as a colorless oil at 102–5 °C (0.03 mmHg) (22.8 g, 56%).

Registry No. **2a**, 111-34-2; **2b**, 109-92-2; **2c**, 16850-55-8; **3a**, 111615-95-3; **3b**, 31172-40-4; **3c**, 114657-08-8; **3d**, 115270-35-4; **3e**, 115270-36-5; **3f**, 115270-37-6; **3g**, 114657-09-9; **3h**, 114657-10-2; **3i**, 114657-11-3; **3j**, 115270-38-7; **3k**, 115270-39-8; (*E*)-**4a**, 36586-17-1; (*Z*)-**4a**, 36586-16-0; (*E*)-**4g**, 97826-86-3; (*Z*)-**4g**, 97826-85-2; **5a**, 56750-84-6; **5g**, 109125-23-7; **6**, 108-05-4; **7**, 100-42-5;

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J. Org. Chem. **1988**, *53*, 4263–4273 **4263**

8, 103-30-0; **9**, 3195-78-6; **10**, 96-33-3; **11**, 614-47-1; **12**, 19522-25-9; **13**, 1754-62-7; (+)-I, 115270-40-1; (–)-I, 115270-41-2; $Pd(OAc)_2$, 3375-31-3; $PdCl_2$, 7647-10-1; $Pd(PhCN)_2Cl_2$, 14220-64-5; Pd, 7440-05-3; (*E,X*)-$H_2NCONHN{=}C(Ph)CH{=}CHOBu$, 115270-34-3; MeO-*m*-$C_6H_4COCl$, 1711-05-3; MeO-*p*-$C_6H_4COCl$, 100-07-2; Cl-*p*-$C_6H_4COCl$, 122-01-0; Br-*p*-$C_6H_4COCl$, 586-75-4; (*E*)-$H_3CC(Ph){=}CHOBu$, 109125-24-8; (*Z*)-$H_3CC(Ph){=}CHOBu$, 109125-26-0; O_2N-*p*-C_6H_4COCl, 122-04-3; (*E*)-O_2N-*p*-$C_6H_4COCH{=}CDOBu$, 115270-43-4; (*E*)-O_2N-*p*-$C_6H_4CH{=}CDOBu$, 115288-63-6; (*E*)-O_2N-*p*-$C_6H_4CD{=}CHOBu$, 115270-44-5; (*Z*)-O_2N-*p*-$C_6H_4CH{=}CDOBu$, 115270-45-6; (*Z*)-O_2N-*p*-$C_6H_4CD{=}CHOBu$, 115270-46-7; (*Z*)-O_2N-*p*-$C_6H_4C(OBu){=}CHD$, 115270-47-8; (*E*)-O_2N-*p*-$C_6H_4C(OBu){=}CHD$, 115270-48-9; benzoyl chloride, 98-88-4; 3,4,5-trimethoxybenzoyl chloride, 4521-61-3; 3-thiophenecarbonyl chloride, 41507-35-1; 3-furancarboxylic acid chloride, 26214-65-3; 2-naphthalenecarboxylic acid chloride, 2243-83-6; 4-nitrobenzoic acid, 62-23-7; butyl α-deuteriovinyl ether, 115270-42-3.

Metalation of Phenols. Synthesis of Benzoquinones by the Oxidative Degradation Approach

José M. Saá,* Antonia Llobera, Angel García-Raso, Antonio Costa, and Pedro M. Deyá

Departament de Química, Universitat de les Illes Balears, E-07071 Palma de Mallorca, Spain

Received November 25, 1987

In an effort to explore the potential of the so-called oxidative degradation approach for the synthesis of quinones, we have investigated the direct metalation of a number of simple phenols such as *o*- and *p*-hydroxybenzyl alcohols, benzyl methyl ethers and *N,N*-dimethylbenzylamines. Apparently, only those phenolic substrates having available both a coordinating group for chelation and an electron-withdrawing group in a 1,3-relationship are efficiently lithiated, by the action of *n*-BuLi, in a regioselective manner. Those positions on the aromatic nucleus just flanked by a coordinating, or an acid–base, group could be metalated by the action of the *t*-BuLi/THP system, in favorable cases.

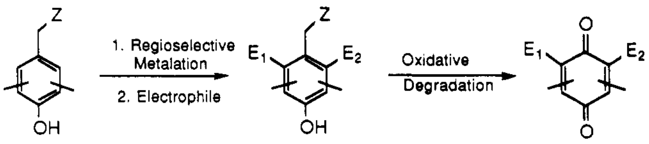
The search for new synthetic approaches for the widespread quinone functionality is a continuously growing area of investigation.[1] In regard to an ongoing research project, we have recently developed a novel route to quinones based on the very simple strategy outlined in Scheme I.[2]

As depicted (Scheme I), there were two main objectives to be reached throughout the work: first, it was essential to develop a novel degradative oxidation of substituted phenols; and second, it was also of prime importance to achieve metalation of substituted phenols in a direct manner.

In a series of recent publications[3] we have shown that several para-substituted phenols, namely *p*-hydroxybenzyl alcohols and *p*-hydroxybenzylamines, as well as some *p*-hydroxybenzoic acids and *p*-hydroxybenzamides, undergo Fremy's salt promoted oxidative degradation to the corresponding quinones. Obviously, the above type of substrates appeared as the most immediate highly promising quinone synthons for our planned synthetic endeavors, provided that our expectations of finding a working protocol for the regioselective functionalization of phenols (via metalation followed by trapping with electrophiles) could be established.

In spite of the outstanding growth of aromatic organolithium chemistry[4] witnessed during the past few years, organolithium derivatives of phenols, or rather lithium phenolates, have remained largely unexplored. Possibly, the lack of success of Gilman et al.[5] in their pioneering studies on the lithiation of simple phenols convinced researchers to resort to the well-established protection/deprotection strategy, whenever a regioselective metalation—and subsequent functionalization—of a phenol were needed. In fact, only very recently[6] the regioselective ortho metalation (*t*-BuLi/THP) of phenol itself has been described.

Scheme I



Therefore we embarked upon a systematic study of the direct metalation of phenols,[7] the results of which are reported herein. We will demonstrate that the direct metalation of phenols is a powerful tactic for the regioselective functionalization of phenolic substrates, thus giving support, at least in part, to the unwritten though nevertheless very familiar synthetic principle: "the best way of protecting a (phenolic) functional group is no protection at all".

Results

At the outset of our work, the metalation of a series of simple *p*-hydroxybenzyl alcohols was attempted in order to find the appropriate conditions not only for achieving ring metalation but also for avoiding undesirable benzylic

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(1) For some recent developments in the area, see: Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilberton, S. R. *Tetrahedron* **1985**, *24*, 5813. Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *24*, 5803.

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