Phenols as *C*- and *O*-Nucleophiles in Palladium-Catalysed Allylic Substitutions

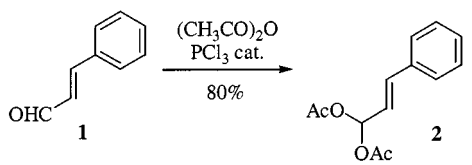
Bastien Nay,[a] Jean-François Peyrat,[a] and Joseph Vercauteren*[a]

Keywords: Palladium / Allyl complexes / Phenolic nucleophiles / Chromene / C–C couplings / Flavonoids

Syntheses of 2-phenyl-2*H*-chromene (3-flavene) and cinnamaldehyde aryloxy-hemiacetal, involving nucleophilic substitution by phenols of the π-allyl palladium complex formed from the acylal of cinnamaldehyde in the presence of catalytic amounts of palladium(0) (10 mol-%), are presented. Alternatively, the corresponding alcohol acetates furnish 1,3-diarylpropenes and cinnamyl aryl ethers. Our results demonstrate the potent *C*-nucleophilicity of phloroglucinol in Tsuji–Trost reactions in flavonoid synthesis, and again illustrate the already well established *O*-nucleophilicity of phenols.

Activated forms of allylic alcohols (esters, carbonates) are very useful precursors of cationic electrophilic "π-allyl palladium" complexes, which allow efficient carbon−carbon bond formation in Tsuji−Trost reactions.[1a−1f] These intermediates have been extensively used in syntheses of many natural products, such as terpenes, alkaloids, cyclopentanoids, steroids, etc.[2a−2c] However, as far as we are aware, π-allyl palladium chemistry has never been applied to the synthesis of chromene-type molecules. Among phenols, only β-naphthol has previously been reported to behave as a *C*-nucleophile in palladium-catalysed reactions with allyl acetates. The compound formed was shown to be the thermodynamic product;[3a,3b] under kinetic conditions (−20°C) only the *O*-allyl derivative was obtained.

As a result of our interest in the total synthesis of natural polyphenols, we have developed a synthetic pathway to 2-phenyl-2*H*-chromene as a flavonoid skeleton precursor. A facile access to flavonoids or neoflavonoids (1,3-diarylpropane or 1,1-diarylpropane framework, respectively) has been developed by Jurd,[4a,4b] employing base-catalysed coupling of polyphenols to cinnamyl alcohol derivatives. We present herein an analogous strategy involving palladium-catalysed substitution of an allylic geminal diacetate **2** by phloroglucinol **3**.[5a−5e] This cinnamaldehyde derivative (acylal **2**) proved to be an ideal substrate for Pd^0-catalysed substitution.[6] The starting material **2** was prepared in 80% yield as a crystalline compound by the method of Michie and Miller[5c] from cinnamaldehyde **1** and acetic anhydride in the presence of catalytic amounts of PCl_3 (Scheme 1).



Scheme 1. Synthesis of cinnamaldehyde diacetyl acylal **2**

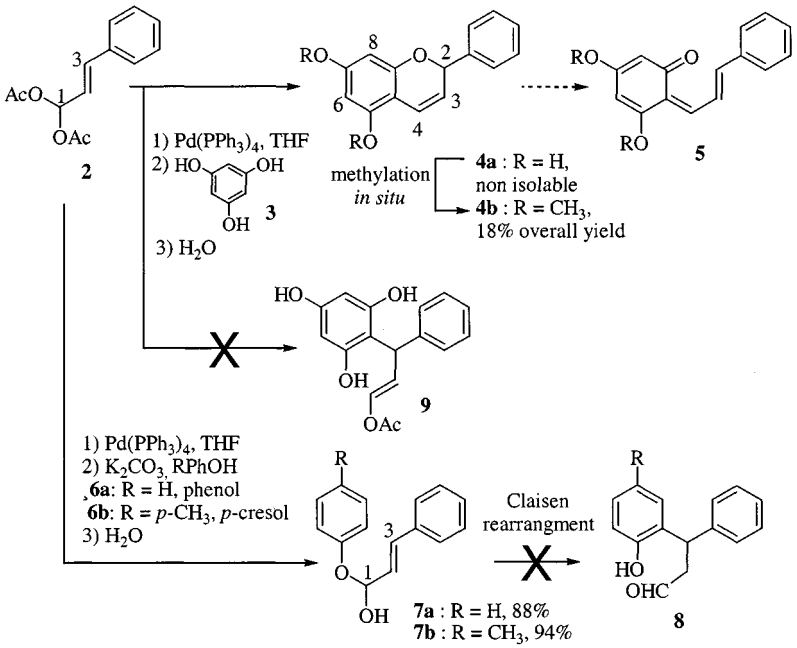
[a] Laboratoire de Pharmacognosie, Faculté de Pharmacie, Université Victor Ségalen Bordeaux 2,
146, rue Léo Saignat, F-33076 Bordeaux, France
Fax: (internat.) +33 (0)5 56 96 09 75
E-mail: Joseph.Vercauteren@gnosie.u-bordeaux2.fr

When acylal **2** was heated above 50°C with various phenols under different conditions, reaction was only found to occur in the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium. In the case of phloroglucinol **3**, the reaction led, after 4 h, to 5,7-dihydroxy-2-phenyl-2*H*-chromene **4a** (Scheme 2). This transformation, however, did not reach completion, even in the presence of an excess of phloroglucinol, owing to a slow hydrolysis of acylal **2** to cinnamaldehyde **1** (10−20%). This hydrolysis could not be avoided, even in the presence of molecular sieves. Unfortunately, all attempts to run this reaction at a lower temperature did not lead to even a trace of the alkylated compound. Thus, it was not possible to investigate whether or not **4a** was the thermodynamic product.

Though the ^{1}H-NMR spectrum of the crude reaction mixture featured the expected signals for chromene **4a** [δ = 5.75 (br. s, 2-H), 5.50 (m, 3-H), 6.00, 6.15 (2× br. s, 6-H, 8-H), 6.90 (d, J = 10 Hz, 4-H)], it proved impossible to purify the product by any method. All attempts led to the decomposition of chromene **4a** to brownish-yellow tars. In order to improve the stability of the adduct, its phenolic functions were protected: the crude mixture containing **4a** was submitted to methylation with CH_3I/K_2CO_3 in DMF. The best results for the purification of flavene **4b** (5,7-dimethoxy-2-phenyl-2*H*-chromene), 18% overall yield, were achieved using alumina as the stationary phase for chromatography.

The low stability of flavene in either form (**4a**, **4b**) may be due to the mutually *meta* arrangement of the two phenolic groups or due to the 2*H*-pyran ring, "Claisen-type" rearrangement of which might lead to the reactive *ortho*-quinone methide **5**. In order to circumvent this problem, monophenols **6a** and **6b** were used with the aim of obtaining more stable unsubstituted chromenes under the same conditions as those used with phloroglucinol **3**. However, even after refluxing in THF for a prolonged reaction time (24 h rather than 4 h), hemiacetals **7a** (31%) and **7b** (42%) were the only adducts formed. These arose from *O*-nucleophilic attack of the phenol on the palladium complex intermediate, with subsequent hydrolysis of the residual

  1434−193X/99/0909−2231 $ 17.50+.50/0



Scheme 2. Reactions of cinnamaldehyde diacetyl acylal **2** with phloroglucinol or simple phenols

acetate (Scheme 2). These hemiacetals are stable, unless they are exposed to acidic or neutral media. We noticed that greatly improved yields of **7a** (88%) and **7b** (94%) were obtained when 8 equivalents of potassium carbonate were added to the reaction mixture. Hemiacetal **7a** was subjected to various conditions conducive to Claisen rearrangement, but in no case gave the expected compound **8**, a precursor of the neoflavonoid-type skeleton. Instead, it was rapidly hydrolysed to the starting cinnamaldehyde and phenol.

Thus, phloroglucinol **3** is a suitable starting material for a one-pot synthesis of flavene. Such compounds have been used by Kawamoto[7] en route to the total synthesis of flavonoids. Phloroglucinol is an eminently suitable phenol for reaction as an aromatic *C*-nucleophile, and can thus be employed in Tsuji−Trost C−C couplings. Reaction of the π-allyl palladium complex of **2** with phloroglucinol **3** allows synthesis of **4a** through a double substitution. The 2*H*-pyran-type heterocycle is formed as a result of the double-site nucleophilicity of phloroglucinol **3**: first the C−C bond is formed at the 1-position, and then *O*-addition at the 3-position forms the heterocyclic ring. Even though the flavene **4a** incorporates an aryl ether of an allylic alcohol, which could act as a substrate forming a π-allyl palladium complex, it remains in the cyclized form. It is worthy of note that the alternative branched product **9** (Scheme 2), resulting from addition of the phenol at the 3-position, was not observed in our case, although it has been isolated by Jurd et al.[4a] in a similar reaction.

We then tried to extend this kind of phloroglucinol reactivity in Pd-catalysed reactions to cinnamyl acetates (Scheme 3). Thus, reaction of phloroglucinol **3** with **10a** under the same conditions led to the C−C bond adduct **11a** (30% yield after purification), while with **6b** the aryl ether **12** (66% yield) was obtained, resembling the products observed by Zanarotti.[8a,8b]

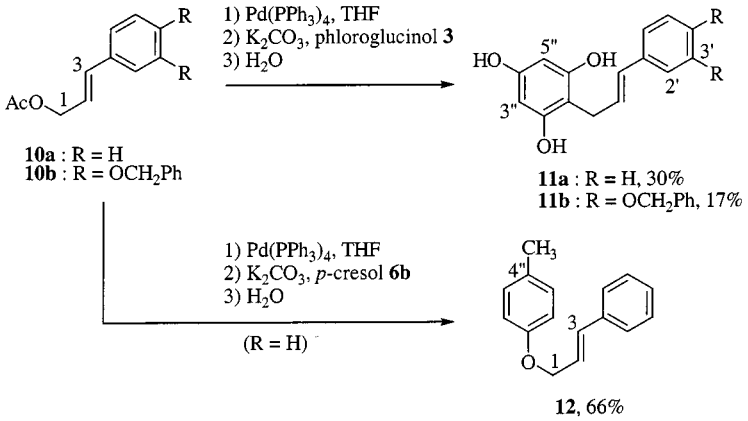
Finally, reaction with the dibenzyl ether of coniferyl acetate (**10b**) yielded the very interesting precursor **11b** (17%), incorporating the framework of flavanol derivatives. This compound has been used to gain access to the catechin series,[9a,9b] of which it thus represents part of a formal synthesis.

Conclusion

Palladium-catalysed C−C bond forming reactions between cinnamyl derivatives and phloroglucinol have been shown to constitute a powerful strategy for the synthesis of flavonoids. As a result of the double reactivity of acylal **2**, and the ambivalent (*C*- and *O*-) nucleophilicity of phloroglucinol **3**, the synthesis of **4b** represents a formal total synthesis of such natural products. Moreover, as has been shown by Trost[10] in the case of acylals, this synthesis of flavenes could be made asymmetric by using chiral ligands of palladium(0) in place of triphenylphosphane.

Experimental Section

General: Palladium-catalysed reactions were carried out using 10 mol-% tetrakis(triphenylphosphane)palladium, generated in situ from $Pd(OAc)_2$ and triphenylphosphane, in freshly distilled THF. Refluxing a THF solution of **2**, **10a** or **10b**, and phenol/K_2CO_3 or phloroglucinol in the presence of $Pd(PPh_3)_4$ led to the described products. Methylation of **4a** was carried out on the crude extract in DMF using CH_3I/K_2CO_3, after removal of the excess phloroglucinol by treatment with dichloromethane/aqueous alkali. Column chromatographic purifications were performed on silica gel, except in the case of **4b**, for which alumina was used. − IR: Bomem MB 100. − UV/vis: Hitachi U2000. − NMR: Bruker AMX-500 (500.13 MHz and 125.03 MHz for ^1H and ^{13}C, respectively). − MS: Finnigan MAT TSQ 700 (triple-stage quadrupole).



Scheme 3. Reactions of cinnamyl acetates with pholoroglucinol or simple phenols

5,7-Dimethoxy-2-phenyl-2*H*-chromene (4b): Overall yield 18%, yellow oil. − IR (thin film): $\tilde{\nu}$ = 2936 cm^{-1} (CH), 1614 (C=C), 1452, 1262, 1204, 1146, 1116, 736. − UV/vis (methanol): λ_{max} = 209 nm, 275, 381. − ^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 7-OCH_3), 3.82 (s, 5-OCH_3), 5.64 (dd, *J* = 9.9, 3.4 Hz, 3-H), 5.86 (dd, *J* = 3.3, 2.0 Hz, 2-H), 6.06 (d, *J* = 2.2 Hz, 6-H), 6.09 (d, *J* = 2.2 Hz, 8-H), 6.84 (dd, *J* = 9.9, 1.9 Hz, 4-H), 7.32 (m, 4′-H), 7.37 (m, 3′-H, 5′-H), 7.47 (m, 2′-H, 6′-H). − ^{13}C NMR ($CDCl_3$): δ = 55.3 (7-OCH_3), 55.6 (5-OCH_3), 77.1 (C-2), 91.9 (C-6), 93.9 (C-8), 104.5 (C-4a), 118.6 (C-4), 119.7 (C-3), 127.0 (C-2′, C-6′), 128.1 (C-4′), 128.5 (C-3′, C-5′), 141.0 (C-1′), 155.0 (C-8a), 156.3 (C-5), 161.3 (C-7). − MS (CI, CH_4); *m/z* (%): 269 [MH^+] (75), 219 (20), 183 (40), 179 (100), 123 (90), 105 (100), 91 (35).

(*E*)-1-Hydroxy-1-phenyloxy-3-phenyl-2-propene (7a): Yield 88%, colourless crystals; m.p. 50−51°C. − IR (thin film): $\tilde{\nu}$ = 3380 cm^{-1} (OH), 3046 (CH), 1669, 1593 (C=C), 1490, 1219 (C−O), 965, 750. − UV/vis (methanol): λ_{max} = 207 nm, 253. − ^{1}H NMR ($CDCl_3$): δ = 6.33 (d, *J* = 5.0 Hz, 1-H), 6.48 (dd, *J* = 16.0, 5.0 Hz, 2-H), 6.95 (d, *J* = 16.0 Hz, 3-H), 7.05 (m, 4′′-H), 7.09 (m, 2′′-H, 6′′-H), 7.29−7.45 (m, 3′′-H, 2′- to 6′-H). − ^{13}C NMR ($CDCl_3$): δ = 100.2 (C-1), 117.8 (C-2′′, C-6′′), 122.6 (C-4′′), 124.7 (C-2), 126.9 (C-2′, C-6′), 128.4 (C-4′), 128.6 (C-3′, C-5′), 129.5 (C-3′′, C-5′′), 134.5 (C-3), 135.7 (C-1′), 156.0 (C-1′′). − MS (FAB+, triethanolamine); *m/z* (%): 209 [$MH^+ - H_2O$] (100).

(*E*)-1-Hydroxy-1-(4′′-methylphenyloxy)-3-phenyl-2-propene (7b): Yield 94%, colourless crystals; m.p. 84°C. − IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (OH), 3024, 2920 (CH), 1663, 1609 (C=C), 1508, 1241 (C−O), 1209, 1175, 1036, 957, 807. − UV/vis (methanol): λ_{max} = 206 nm, 251. − ^{1}H NMR ($CDCl_3$): δ = 2.34 (s, 4′′-CH_3), 6.27 (dd, *J* = 5.0, 0.9 Hz, 1-H), 6.50 (dd, *J* = 16.1, 5.0 Hz, 2-H), 6.95 (d, *J* = 16.1 Hz, 3-H), 7.02 (m, 2′′-H, 6′′-H), 7.13 (m, 3′′-H, 5′′-H), 7.32 (m, 4′-H), 7.37 (m, 3′-H, 5′-H), 7.47 (m, 2′-H, 6′-H). − ^{13}C NMR ($CDCl_3$): δ = 20.5 (4′′-CH_3), 100.8 (C-1), 117.9 (C-2′′, C-6′′), 125.1 (C-2), 127.0 (C-2′, C-6′), 128.4 (C-4′), 128.6 (C-3′, C-5′), 130.0 (C-3′′, C-5′′), 132.0 (C-4′′), 134.3 (C-3), 135.8 (C-1′), 154.0 (C-1′′). − MS (FAB+, triethanolamine); *m/z* (%): 223 [$MH^+ - H_2O$] (100).

(*E*)-1-(4′′-Methylphenyloxy)-3-phenyl-2-propene (12): Yield 66%, white crystals; m.p. 76−77°C. − IR (thin film): $\tilde{\nu}$ = 3020 cm^{-1}, 2916 (CH), 1610 (C=C), 1518, 1384, 1240 (C−O), 1006, 964, 814, 730. − UV/vis (methanol): λ_{max} = 208 nm, 249. − ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 4′′-CH_3), 4.72 (d, *J* = 5.7 Hz, 1-CH_2), 6.51 (dt, *J* = 15.9, 5.7 Hz, 2-H), 6.77 (d, *J* = 15.9 Hz, 3-H), 6.92 (d, *J* = 8.5 Hz, 2′′-H, 6′′-H), 7.14 (d, *J* = 8.5 Hz, 3′′-H, 5′′-H), 7.30 (m, 4′-H), 7.37 (m, 3′-H, 5′-H), 7.45 (m, 2′-H, 6′-H). − ^{13}C NMR ($CDCl_3$): δ = 20.5 (4′′-CH_3), 68.1 (C-1), 114.9 (C-2′′, C-6′′), 125.0 (C-2), 126.6 (C-2′, C-6′), 127.8 (C-4′), 128.6 (C-3′, C-5′), 130.0 (C-3′′, C-5′′), 130.1 (C-4′′), 132.8 (C-3), 136.7 (C-1′), 156.7 (C-1′′). − MS (CI, CH_4); *m/z* (%): 224 [M^+] (70), 118 (50), 117 (100), 91 (55).

(*E*)-1-Phenyl-3-(2′′,4′′,6′′-trihydroxyphenyl)-1-propene (11a): Yield 30%, yellow oil. − IR (thin film): $\tilde{\nu}$ = 3396 cm^{-1} (OH), 2940 (CH), 1460, 1380, 1278, 1152, 820, 740. − UV/vis (methanol): λ_{max} = 212 nm, 251. − ^{1}H NMR ($CDCl_3$): δ = 3.49 (dd, *J* = 6.1, 0.9 Hz, 3-CH_2), 5.96 (s, 3′′-H, 5′′-H), 6.33 (dt, *J* = 15.9, 6.0 Hz, 2-H), 6.43 (d, *J* = 15.9, 1-H), 7.14 (m, 4′-H), 7.23 (m, 3′-H, 5′-H), 7.29 (m, 2′-H, 6′-H). − ^{13}C NMR ($CDCl_3$): δ = 29.6 (3-CH_2), 95.8 (C-3′′, C-5′′), 105.1 (C-1′′), 126.1 (C-2′, C-6′), 126.9 (C-4′), 128.3 (C-3′, C-5′), 128.5 (C-2), 130.2 (C-1), 137.4 (C-1′), 155.4 (C-4′′), 155.9 (C-2′′, C-6′′). − MS (CI, CH_4); *m/z* (%): 242 [M^+] (90), 138 (45), 117 (50), 91 (100).

(*E*)-1-(3′,4′-Dibenzyloxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-1-propene (11b): Yield 17%, yellow oil. − IR (thin film): $\tilde{\nu}$ = 3408 cm^{-1} (OH), 2940 (CH), 1504, 1452, 1380, 1262, 1138, 1014, 736. − UV/vis (methanol): λ_{max} = 219 nm, 262. − ^{1}H NMR ($CDCl_3$): δ = 3.46 (d, *J* = 5.6 Hz, 3-H), 5.08 (s, 3′-OCH_2), 5.10 (s, 4′-OCH_2), 5.94 (s, 3′′-H, 5′′-H), 6.13 (dt, *J* = 15.8, 5.6 Hz, 2-H), 6.36 (d, *J* = 15.8 Hz, 1-H), 6.82 (m, 2′-H, 5′-H), 6.96 (m, 6′-H), 7.26−7.43 (m, 10 benzylic H). − ^{13}C NMR ($CDCl_3$): δ = 26.1 (C-3), 71.5 (2 benzylic OCH_2), 96.1 (C-3′′, C-5′′), 105.2 (C-1′′), 113.1 (C-6′), 115.4 (C-5′), 119.9 (C-2′), 126.8 (C-2), 127.4, 127.5, 127.7, 128.4 (10 benzylic C−H), 129.9 (C-1), 131.4 (C-1′), 137.2 (2 benzylic C-*ipso*), 148.3 (C-4′), 149.0 (C-3′), 155.1 (C-4′′), 155.7 (C-2′′, C-6′′). − MS (CI, CH_4); *m/z* (%): 454 [M^+] (50), 91 (100).

Acknowledgments

We thank the MENRT and the ONIVins for financial support. One of us (B. N.) gratefully acknowledges receipt of a scholarship from the MENRT.

[1] [1a] J. Tsuji, *Palladium Reagents and Catalysts*, 1st. ed., John Wiley & Sons, New York, **1995**, pp. 290−406. − [1b] J. Tsuji, *Pure & Appl . Chem*. **1982**, *54*, 197−206. − [1c] J. Tsuji, *Tetrahedron* **1986**, *42*, 4361−4401. − [1d] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395−422. − [1e] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385−393. − [1f] B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3416−3426.

[2] [2a] B. M. Trost, L. Weber, *J. Org. Chem*. **1975**, *40*, 3618−3619. − [2b] B. M. Trost, J. P. Genêt, *J. Am. Chem. Soc.* **1976**, *98*,

1816−1817. − [2c] B. M. Trost, P. Renaud, *J. Am. Chem. Soc.* **1982**, *104*, 6668−6672.
[3] [3a] G. Balavoine, G. Bram, F. Guibe, *Nouv. J. Chim.* **1978**, *2*, 207−209. − [3b] C. Goux, M. Massacret, P. Lhoste, D. Sinou, *Organometallics* **1995**, *14*, 4585−4593.
[4] [4a] L. Jurd, J. N. Roitman, *Tetrahedron* **1978**, *34*, 57−62. − [4b] G. Cardillo, R. Cricchio, L. Merlini, *Tetrahedron Lett.* **1969**, 907−908.
[5] [5a] I. Scriabine, *Bull. Soc. Chim. Fr.* **1961**, *185*, 1194−1198. − [5b] G. Saucy, R. Marbet, H. Lindlar, O. Isler, *Helv. Chim. Acta* **1959**, *42*, 1945−1955. − [5c] J. K. Michie, J. A. Miller, *Synthesis* **1981**, 824. − [5d] K. S. Kochhar, B. S. Bal, R. P. Deshpande, S. N. Rajadhyaksha, H. W. Pinnick, *J. Org. Chem.* **1983**, *48*, 1765−1767. − [5e] N. Deka, D. J. Kalita, R. Borah, J. C. Sarma, *J. Org. Chem.* **1997**, 1563−1564.
[6] B. M. Trost, J. Vercauteren, *Tetrahedron Lett.* **1985**, *26*, 131−134.
[7] H. Kawamoto, F. Nakatsubo, K. Murakami, *J. Wood Chem. Technol.* **1989**, *9*, 35−52.
[8] [8a] A. Zanarotti, *Tetrahedron Lett.* **1982**, *23*, 3963−3964. − [8b] A. Zanarotti, *Tetrahedron Lett.* **1982**, *23*, 3815−3818.
[9] [9a] H. Van Rensburg, P. S. Van Heerden, D. Ferreira, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3415−3421. − [9b] H. Van Rensburg, P. S. Van Heerden, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron Lett.* **1997**, *38*, 3089−3092.
[10] B. M. Trost, C. B. Lee, J. M. Weiss, *J. Am. Chem. Soc.* **1995**, *117*, 7247−7248.

Received January 12, 1999
[O99038]