Salt-free C–C coupling reactions of arenes: palladium-catalyzed telomerization of phenols[1]

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A salt-free functionalisation of phenols with either butadiene or isoprene in the presence of palladium catalysts has been developed, which gives octadienyl- or decadienylphenols selectively.

Transition metal-catalyzed C–C coupling reactions of arenes with unsaturated organic compounds are of increasing importance for the synthesis of fine chemicals, agrochemicals and intermediates for pharmaceuticals.[2] However, a general problem in most arene transformation reactions is the production of at least stoichiometric amounts of salts due to the necessity of using Lewis acids or suitable activating groups, *e.g.* halides, on the aromatic ring. Despite considerable efforts in the past, only a few examples of direct atom-efficient functionalizations of aromatic compounds are known.[3] Hence, the development of efficient ecologically-favorable protocols for the construction of C–C bonds to aromatic rings is one of the important goals for catalysis.

In 1967 Smutny[4] described the first palladium-catalyzed telomerization reaction[5] of phenol with buta-1,3-diene, which yielded *O*-allylated octa-2,7-dienyl ethers. In the original paper Smutny also reported the observation of *C*-allylated phenols, although neither product yields nor the reaction conditions were given. Later on, telomerizations with phenol were studied by Weigert,[6] Beger[7] and Kaneda *et al.*[8] In all these studies only the corresponding *O*-allylated ethers were obtained.

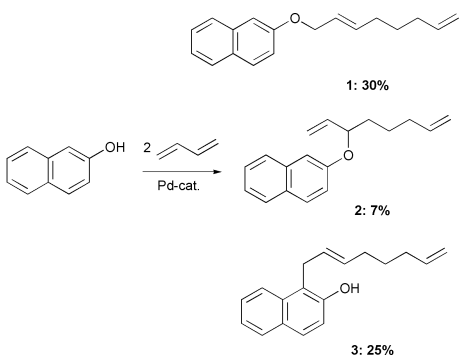
In this paper we describe the catalytic salt-free reaction of naphthol and electron-rich phenols with buta-1,3-diene and 1,3-isoprene giving selectively *C*-allylated phenols.

While studying the telomerization of buta-1,3-diene with methanol,[1] we became interested in the reaction of 1,3-dienes with substituted phenols and naphthol. Applying our previously optimized conditions (0.1 mol% $Pd(OAc)_2$–1 eq. PPh_3 in THF at 90 °C) the reaction of 100 mmol β-naphthol with 200 mmol buta-1,3-diene yielded both of the expected *O*-allylated products (1-naphthoxyocta-2,7-diene **1**: 30% yield and 3-naphthoxyocta-1,7-diene **2**: 7% yield) as well as significant amount (25%) of the *ortho*-*C*-allylated product 1-(octa-2,7-dienyl)-2-naphthol **3** (Scheme 1).

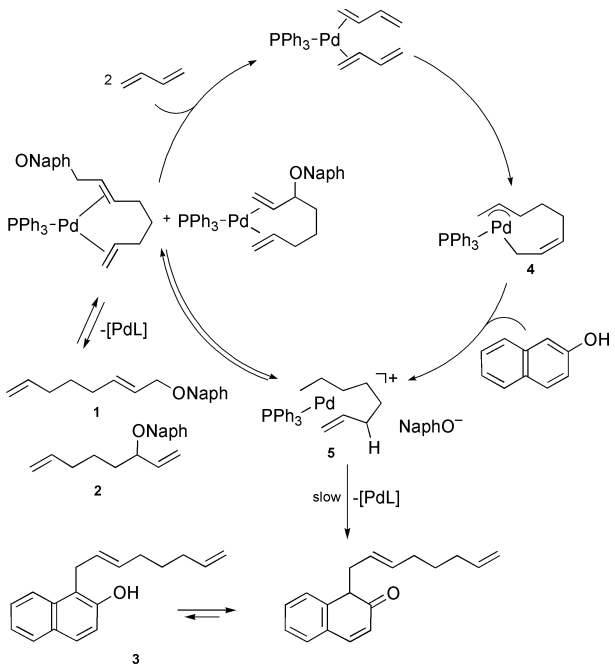
By variation of the catalyst system, the reaction temperature and the ligand-to-metal ratio we discovered that it is possible to obtain the *C*-allylated products selectively (Table 1). Using optimized conditions (L : Pd = 3 : 1; addition of 1 mol% triethylamine) **3** was obtained in 84% yield (ratio C : O-allylated products = > 50 : 1).† Interestingly, this reaction, which resembles the classic Friedel–Crafts allylation, proceeds with high regioselectivity. Apart from **3**, only a small amount (< 3%) of a second *C*-allylated naphthol was obtained. The efficiency of the simple $Pd(OAc)_2$–PPh_3 catalyst is remarkable: even in the presence of only 0.01 mol% Pd-catalyst, a 76% yield of **3** was obtained (TON = 7600).

In order to understand the formation of the *C*-allylated telomerization product we studied the reaction of **1** in the presence of catalytic amounts (0.5 mol%) of $Pd(OAc)_2$–2 PPh_3 in toluene at 70–90 °C. After 30 min at 70 °C none of the *C*-allylated product **3** was observed. However, after 1.5 h at 90 °C the formation of **3** began, and after 6 h (90 °C) **3** was the main product in the reaction mixture, although other *C*-allylated products (*ca.* 5–10%) were detected. Based on detailed mechanistic studies of the telomerization of butadiene and methanol[9] we propose the following mechanism for the formation of **3** (Scheme 2).

The $Pd(0)$-catalyzed dimerization of buta-1,3-diene affords the L–Pd–(η^1,η^3-octadiendiyl) complex **4**. Subsequent protonation at C6 and attack of the oxygen atom at C1 or C3 yields the corresponding naphthyl allyl ethers **1** and **2**. Due to the improved leaving group ability of naphthol compared to an aliphatic alcohol, **1** and **2** are in equilibrium with **5** under the reaction conditions.[10] Allylation is also possible *ortho* to the hydroxy group, due to the ambident character of napthol. As this reaction step is irreversible, **3** is the main product of this reaction. The large influence of the P : Pd-ratio on the yield of **3**



Scheme 1



Scheme 2

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Table 1 Telomerization of buta-1,3-diene with β-naphthol[a]

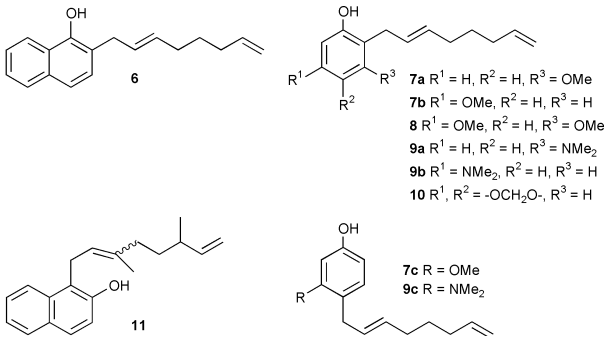
Entry	Ligand	L : Pd	Conversion[b] (%)	Yield **3**[c] (%)	Selectivity **3** (%)	Ratio (**3**) : (**1** + **2**)[d]
1	PPh_3	1:1	75	25	33	1
2	**PPh_3**	**3 : 1**	**82**	**76**	**93**	**38**
3	PPh_3	10 : 1	94	75	80	9
4	PPh_3	50 : 1	75[e]	32	42	5
5	PCy_3	3 : 1	73	38	52	2
6	$P(C_6H_2(OMe)_3)_3$[f]	3 : 1	0	—	—	—
7	$P(t\text{Bu})_3$	3 : 1	0	—	—	—
8	$P(OC_6H_3(C_4H_9)_3)_3$[g]	3 : 1	57	16	29	0.3
9[h]	PPh_3	3 : 1	90	8	9	0.1
10[i]	PPh_3	3 : 1	88	69	78	29
11[j]	**PPh_3**	**3 : 1**	**91**	**84**	**92**	**76**

[a] 100 mmol β-naphthol, 200 mmol buta-1,3-diene, 0.1 mol% $Pd(OAc)_2$, 50 ml THF, T = 90 °C, 16 h. [b] Conversion based on β-naphthol. [c] GC-purity > 80%. [d] Ratio of peak areas (GC) (**3**) : (**1** + **2**). [e] *C*-Alkylated products with only one butadiene unit were also formed. [f] Tris(trimethoxyphenyl)phosphine. [g] Tris(2,4-di-*tert*-butylphenyl) phosphite. [h] 60 °C. [i] 120 °C. [j] Addition of 1.0 mol% NEt_3.

Table 2 Telomerization of buta-1,3-dienes with different substrates[a]

Entry	Educt	Ligand	Product	Yield[b] (%)	Ratio C : O-alk[c]
1	α-Naphthol[d]	PCy_3	**6**	47	> 98 : 2
2	β-Naphthol[e]	PPh_3	**3**	84[f]	> 98 : 2
3	Resorcinol monomethyl ether	PCy_3	**7a–c**	63	> 98 : 2
4	Phloroglucinol dimethyl ether[g]	PPh_3	**8**	72	> 98 : 2
5	3-Dimethylaminophenol	PPh_3	**9a–c**	41	> 98 : 2
6	3,4-Methylenedioxyphenol[h]	PCy_3	**10**	46[f]	> 98 : 2
7	β-Naphthol[i]	PCy_3	**11**	55	> 98 : 2

[a] 100 mmol ROH, 200 mmol buta-1,3-diene, 90 °C, 16 h, THF, 0.5 mol% $Pd(OAc)_2$, Pd : PR_3 1 : 3, NEt_3. [b] GC-purity > 98%. [c] Ratio of peak areas (GC). [d] 12 h. [e] 0.1 mol% $Pd(OAc)_2$. [f] GC-purity > 80%. [g] 12 h, toluene, 0.01 mol% $Pd(OAc)_2$. [h] 150 mmol ROH were used. [i] Isoprene was used instead of buta-1,3-diene, 100 °C, toluene, 1 mol% $Pd(OAc)_2$, isoprene–ROH 3 : 1.



is explained by a deactivation of the Pd catalyst at a low ligand concentration and an inhibition of the catalyst activity in the presence of an excess of phosphine ligand.

In order to demonstrate the generality of the palladium-catalyzed *C*-allylation of phenols we studied the reaction of buta-1,3-diene with electron-rich phenols and the reaction of β-naphthol with isoprene (Table 2). *C*-Allylations similar to β-naphthol are observed with 3-methoxyphenol, 3,5-dimethoxyphenol, α-naphthol, 3-dimethylaminophenol and 3,4-methylenedioxyphenol. In contrast phenol yielded only the corresponding *O*-allylated ethers.

Similar to electrophilic aromatic substitutions, the reaction of butadiene and 3-methoxyphenol, 3,4-methylenedioxyphenol and 3-dimethylaminophenol, gave not only the *ortho*-*C*-allylated products **6**–**10**, but also the *para*-allylated compounds **7c** and **9c**.

The reaction of β-naphthol with isoprene proceeds regioselectively to give the C1-substituted β-naphthol.

In conclusion, we have shown that electron-rich phenols react with 2 molecules of 1,3-dienes in the presence of Pd catalysts to give *C*-allylated phenols. After reduction with hydrogen and Pd/C the corresponding alkylated products are obtained in high yields. The telomerization of phenols with dienes constitutes a salt-free functionalisation of the aromatic nucleus, which proceeds with remarkable catalyst turnover numbers.

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Notes and references

† To a solution of 79 mg (0.3 mmol) triphenylphosphine in 50 ml anhydrous THF in a 100 ml Schlenk tube under an argon atmosphere were added 23 mg (0.1 mmol) palladium acetate and 100 mg (1.0 mmol) triethylamine. The mixture was transferred into a steel autoclave charged with 14.4 g (100 mmol) β-naphthol. After cooling with dry ice 11.0 g (200 mmol) of butadiene were condensed in the autoclave. The reaction was carried out by stirring at 90 °C. After the reaction the resulting residue was purified by flash chromatography (hexane–ethyl acetate) to afford 21.1 g (84%) of **3**.

3: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.29 (m, 2H), 1.88 (pseudo-q, J = 7.5 Hz, 3H), 3.66 (s, 2H), 4.80 (dd, J = 10.0, 2.0 Hz, 1H), 4.84 (dd, J = 17.2, 2.0 Hz, 1H), 5.40 (dt, J = 14.6, 7.1 Hz, 1H), 5.53 (dt, J = 15.1, 6.0 Hz, 1H), 5.60 (ddt, J = 17.1, 10.0, 6.5 Hz, 1H), 5.83 (bs, 1H), 6.96 (d, J = 8.5 Hz, 1H), 7.19 (ddd, J = 8.5, 7.0, 1.0 Hz, 1H), 7.34 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 28.13, 28.45, 31.75, 33.12, 114.36, 117.66, 117.94, 122.86, 123.04, 126.18, 127.58, 127.91, 128.42, 129.26, 131.55, 133.20, 138.63, 151.28.
MS: m/z: 252 [M^+], 157 [$M^+ - C_7H_{11}$] (100).

1 Part 15 of the series, *Palladium-catalyzed Synthesis of Fine Chemicals*, for part 14 see: F. Vollmüller, S. Klein, J. Krause, W. Mägerlein and M. Beller, *Eur. J. Inorg. Chem.*, 2000, 1825.
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