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Heck reactions of aryl bromides with alk-1-en-3-ol derivatives catalysed by a tetraphosphine/palladium complex

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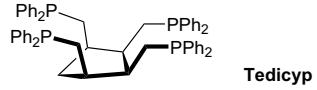
Abstract—*cis*,*cis*,*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ efficiently catalyses the Heck reaction of alk-1-en-3-ol with a variety of aryl bromides. In the presence of hex-1-en-3-ol or oct-1-en-3-ol, the β-arylated carbonyl compounds were selectively obtained. Linalool and 2-methylbut-3-en-2-ol led to the corresponding 1-arylalk-1-en-3-ol derivatives. Turnover numbers up to 69,000 can be obtained for this reaction. A minor electronic effect of the substituents of the aryl bromide was observed. Similar reaction rates were observed in the presence of activated aryl bromides such as bromoacetophenone and deactivated aryl bromides such as bromoanisole.

The palladium-catalysed Heck vinylation reaction is one of the most powerful methods for the formation of C–C bonds.[1] The efficiency of several catalysts for the reaction of aryl halides with acrylates or styrene derivatives has been studied in detail.[2] On the other hand, the reaction in the presence of alk-1-en-3-ol has attracted less attention. Moreover, most of the results described with these alkenes were obtained in the presence of expensive aryl iodides.[3] Few results have been described in the presence of aryl bromides.[4–7] The reaction of alk-1-en-3-ol and aryl bromides can be performed with a Pd/triphenylphosphine catalyst, but the palladium complexes formed with this ligand are generally not very efficient in terms of substrate/catalyst ratio.[4] This reaction also proceeds in the presence of $Pd(OAc)_2$ or $PdCl_2$ without added ligand, but 5% catalyst were used.[5,6] In recent years, a more efficient catalyst has been tested with these substrates by Calo et al. They described that a Pd-benzothiazole carbene complex catalyses the reaction of but-1-en-3-ol, pent-1-en-3-ol or oct-1-en-3-ol with aryl bromides in the presence of 1% catalyst.[7] If monophosphine or carbene ligands have been successfully used for the reaction with these alkenes, to the best of our knowledge, the efficiency of tetraphosphine ligands has not been demonstrated.

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[8] (Fig. 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,[8] for Suzuki cross-coupling[9] and for Sonogashira alkynylation[10] using tedicyp as the ligand. We have also reported several results for Heck vinylation.[11] In order to further establish the requirements for a successful Heck reaction with our catalyst, we herein report on the reaction of aryl bromides with alk-1-en-3-ol derivatives.

For this study, based on previous results,[11] DMF was chosen as the solvent and K_2CO_3 as the base. The reactions were performed at 130 °C under argon in the presence of a 1:2 ratio of $[Pd(C_3H_5)Cl]_2$/tedicyp as catalyst.



Tedicyp

Figure 1.

Keywords: Palladium; Catalysis; Heck reaction; Tetraphosphine.
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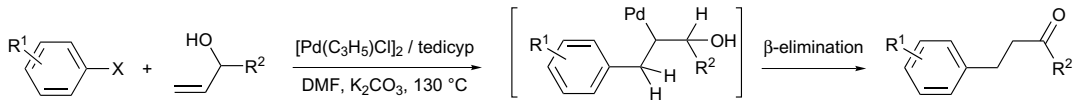
We first studied the reactivity of hex-1-en-3-ol with several aryl halides in the presence of 0.1–0.001 mol% catalyst (Scheme 1, Table 1). It is known that the Heck reaction in the presence of alk-1-en-3-ol often leads to the formation of β-arylated ketones.[3a] With our catalyst, these ketones were obtained selectively in all cases indicating that the Pd-tedicyp catalyst is probably a neutral complex favouring β-elimination to form the corresponding enol rather than the β-aryl allylic alcohol.[1b] We observed that tedicyp-Pd catalyst system is tolerant of a variety of aryl halides. Surprisingly, iodobenzene led to the coupling adduct in a lower turn over numbers (TON) than the reaction performed in the presence of 4-*t*-butylbromobenzene (Table 1, entries 1, 10 and 11). A minor influence of the electronic factors of the aryl bromide on the reaction rate was also observed. Similar TONs were observed using activated 4-bromoacetophenone and deactivated 4-bromoanisole: 69,000 and 84,000, respectively (Table 1, entries 2, 3, 12 and 13) indicating that the rate-limiting step of the reaction with these alkenols is not the oxidative addition of the aryl bromide. The reaction performed with the *ortho*-substituted aryl bromides 2-trifluoromethyl-bromobenzene or 2-methylbromobenzene led to similar TONs of 33,000 and 7500 than the *para*-substituted arylbromides (Table 1, entries 14–19).

Very similar reaction rates were obtained for the coupling of aryl bromides with oct-1-en-3-ol (Table 1, entries 22–28).

Heteroaromatic substrates such as 3-bromopyridine, or bromothiophenes in the presence of hex-1-en-3-ol or oct-1-en-3-ol also led to the expected adducts in good yields (Table 1, entries 20, 21, 27 and 28).

Having demonstrated that linear alk-1-en-3-ol derivatives can be reacted efficiently with aryl bromides, we



R^1 = H, Me, *t*Bu, OMe, MeCO, PhCO, CHO, CF_3, F
R^2 = nC_3H_7, nC_5H_{11}

Scheme 1.

Table 1. Heck reactions with hex-1-en-3-ol or oct-1-en-3-ol catalysed by the tedicyp-palladium complex (Scheme 1)[12]

Entry	Aryl halide	Alkene	Ratio substrate/catalyst	Product	Yield (%)[a]
1	Iodobenzene	Hex-1-en-3-ol	1000	1-Phenylhexan-3-one	78
2	4-Bromoacetophenone	Hex-1-en-3-ol	1000	1-(4-Acetylphenyl)hexan-3-one	85 (100)
3	4-Bromoacetophenone	Hex-1-en-3-ol	10,000	1-(4-Acetylphenyl)hexan-3-one	(69)
4	4-Bromobenzophenone	Hex-1-en-3-ol	10,000	1-(4-Benzoylphenyl)hexan-3-one	91 (100)
5	4-Bromobenzophenone	Hex-1-en-3-ol	100,000	1-(4-Benzoylphenyl)hexan-3-one	(69)
6	4-Trifluoromethylbromobenzene	Hex-1-en-3-ol	1000	1-(4-Trifluorophenyl)hexan-3-one	92 (100)
7	4-Trifluoromethylbromobenzene	Hex-1-en-3-ol	10,000	1-(4-Trifluorophenyl)hexan-3-one	(83)
8	4-Fluorobromobenzene	Hex-1-en-3-ol	1000	1-(4-Fluorophenyl)hexan-3-one	(100)
9	4-Fluorobromobenzene	Hex-1-en-3-ol	10,000	1-(4-Fluorophenyl)hexan-3-one	84
10	4-*t*-Butylbromobenzene	Hex-1-en-3-ol	1000	1-(4-*t*-Butylphenyl)hexan-3-one	(97)
11	4-*t*-Butylbromobenzene	Hex-1-en-3-ol	10,000	1-(4-*t*-Butylphenyl)hexan-3-one	83
12	4-Bromoanisole	Hex-1-en-3-ol	1000	1-(4-Anisyl)hexan-3-one	(100)
13	4-Bromoanisole	Hex-1-en-3-ol	10,000	1-(4-Anisyl)hexan-3-one	84
14	2-Fluorobromobenzene	Hex-1-en-3-ol	10,000	1-(2-Fluorophenyl)hexan-3-one	94 (100)
15	2-Fluorobromobenzene	Hex-1-en-3-ol	100,000	1-(2-Fluorophenyl)hexan-3-one	(67)
16	2-Trifluoromethylbromobenzene	Hex-1-en-3-ol	10,000	1-(2-Trifluorophenyl)hexan-3-one	90 (100)
17	2-Trifluoromethylbromobenzene	Hex-1-en-3-ol	100,000	1-(2-Trifluorophenyl)hexan-3-one	(33)
18	2-Methylbromobenzene	Hex-1-en-3-ol	1000	1-(2-Methylphenyl)hexan-3-one	93 (100)
19	2-Methylbromobenzene	Hex-1-en-3-ol	10,000	1-(2-Methylphenyl)hexan-3-one	(75)
20	3-Bromopyridine	Hex-1-en-3-ol	10,000	1-(3-Pyridyl)hexan-3-one	91 (100)
21	3-Bromopyridine	Hex-1-en-3-ol	100,000	1-(3-Pyridyl)hexan-3-one	(31)
22	4-Bromobenzophenone	Oct-1-en-3-ol	10,000	1-(4-Benzoylphenyl)octan-3-one	(100)
23	4-Bromobenzophenone	Oct-1-en-3-ol	50,000	1-(4-Benzoylphenyl)octan-3-one	80
24	4-Fluorobromobenzene	Oct-1-en-3-ol	10,000	1-(4-Flurophenyl)octan-3-one	89 (100)
25	4-*t*-Butylbromobenzene	Oct-1-en-3-ol	1000	1-(4-*t*-Butylphenyl)octan-3-one	84 (100)
26	4-*t*-Butylbromobenzene	Oct-1-en-3-ol	10,000	1-(4-*t*-Butylphenyl)octan-3-one	(62)
27	2-Bromothiophene	Oct-1-en-3-ol	10,000	1-(2-Thiophene)octan-3-one	92 (100)
28	3-Bromothiophene	Oct-1-en-3-ol	250	1-(3-Thiophene)octan-3-one	73 (80)

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp 1:2 see Ref. 8 ArX (1 equiv), allylic alcohol (2 equiv), K_2CO_3 (2 equiv), DMF, 20 h, 130 °C, under argon, isolated yields, ratio substrate/catalyst based on the aryl halide, in a few cases traces of 1-arylalk-1-en-3-ol derivatives were observed.
[a] Yields in parenthesis correspond to GC and NMR yields.

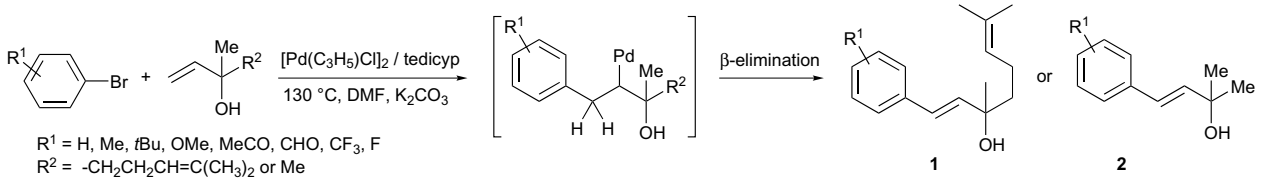
investigated the scope of this coupling reaction using substituted alk-1-en-3-ol derivatives. We studied the reactivity of two 3-substituted alk-1-en-3-ols: linalool and 2-methylbut-3-en-2-ol (Scheme 2, Table 2). With these substituted alkenols the expected 1-arylalk-1-en-3-ol **1** or **2** were obtained selectively but slower reactions were observed than with the unsubstituted alkenol. Linalool led to the expected the coupling adducts in TONs of 740-9000. The results presented in Table 2 unfold a minor substituent effect of the aryl bromide on the reaction rate (Table 2, entries 2–11).

For example, TONs of 8400 can be achieved with this catalyst for the reaction of linalool with the activated substrate 4-bromoacetophenone and with the deactivated substrate 4-bromoanisole (Table 2, entries 2, 3, 10 and 11).

We also studied the influence of *ortho*-substituents on the aryl bromide for this reaction. 2-Fluorobromobenzene, 2-trifluoromethylbromobenzene and 2-methylbromo-benzene led to similar TONs than the *para*-substituted aryl bromides (Table 2, entries 12–17).

The reactivity of 2-methylbut-3-en-2-ol is very similar to linalool and the expected 1-aryl-3-methylbut-1-en-3-ol **2** were obtained in good yields and TONs (Table 2, entries 22–29).

In summary, in the presence of the tedicyp/palladium complex, the Heck vinylation of several aryl bromides with alk-1-en-3-ol derivatives can be performed with as little as 0.01 mol% catalyst. The products of the reactions depend on the substituents of the alkenes. Addition to linalool or 2-methylbut-3-en-2-ol led to the



Scheme 2.

Table 2. Heck reactions with linalool or 2-methylbut-3-en-2-ol catalysed by the tedicyp-palladium complex (Scheme 2)[12]

Entry	Aryl halide	Alkene	Product	Ratio substrate/catalyst	Yield (%)[a]
1	Iodobenzene	Linalool	**1**	1000	69 (74)
2	4-Bromoacetophenone	Linalool	**1**	1000	(100)
3	4-Bromoacetophenone	Linalool	**1**	10,000	84
4	4-Bromobenzaldehyde	Linalool	**1**	1000	78 (83)
5	4-Trifluoromethylbromobenzene	Linalool	**1**	1000	93 (100)
6	4-Fluorobromobenzene	Linalool	**1**	1000	(100)
7	4-Fluorobromobenzene	Linalool	**1**	10,000	81 (87)
8	4-*t*-Butylbromobenzene	Linalool	**1**	1000	(100)
9	4-*t*-Butylbromobenzene	Linalool	**1**	10,000	90
10	4-Bromoanisole	Linalool	**1**	1000	(100)
11	4-Bromoanisole	Linalool	**1**	10,000	84
12	2-Fluorobromobenzene	Linalool	**1**	1000	(100)
13	2-Fluorobromobenzene	Linalool	**1**	10,000	88
14	2-Trifluoromethylbromobenzene	Linalool	**1**	1000	91 (100)
15	2-Trifluoromethylbromobenzene	Linalool	**1**	10,000	(54)
16	2-Methylbromobenzene	Linalool	**1**	1000	87 (100)
17	2-Methylbromobenzene	Linalool	**1**	10,000	(69)
18	3-Bromopyridine	Linalool	**1**	1000	86 (100)
19	3-Bromopyridine	Linalool	**1**	10,000	(75)
20	2-Bromothiophene	Linalool	**1**	1000	82 (92)
21	3-Bromothiophene	Linalool	**1**	1000	83 (90)
22	4-Trifluoromethylbromobenzene	2-Methylbut-3-en-2-ol	**2**	1000	90 (98)[b]
23	4-Bromobenzophenone	2-Methylbut-3-en-2-ol	**2**	10,000	93 (100)[b]
24	4-Fluorobromobenzene	2-Methylbut-3-en-2-ol	**2**	1000	78[b]
25	4-*t*-Butylbromobenzene	2-Methylbut-3-en-2-ol	**2**	250	(97)[b]
26	4-*t*-Butylbromobenzene	2-Methylbut-3-en-2-ol	**2**	1000	77 (81)[b]
27	4-Bromoanisole	2-Methylbut-3-en-2-ol	**2**	1000	90 (100)[b]
28	4-Bromoanisole	2-Methylbut-3-en-2-ol	**2**	10,000	(68)[b]
29	2-Methylbromobenzene	2-Methylbut-3-en-2-ol	**2**	1000	78 (86)[b]

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp 1:2 see Ref. 8 ArX (1 equiv), allylic alcohol (2 equiv), K_2CO_3 (2 equiv), DMF, 20 h, 130 °C, under argon, isolated yields, ratio substrate/catalyst based on the aryl halide.

[a] Yields in parenthesis correspond to GC and NMR yields.

[b] Reactions performed in an autoclave.

corresponding 1-aryl-alk-1-en-3-ol **1** or **2**. In the presence of hex-1-en-3-ol or oct-1-en-3-ol the β-arylated carbonyl compounds were obtained. Higher reactions rates were observed with the unsubstituted alk-1-en-3-ol. In general, the rate-limiting step of these reactions does not seem to be the oxidative addition of the aryl halides. With these alk-1-en-3-ol derivatives similar reaction rates were observed in the presence of 4-bromoacetophenone or 4-bromoanisole. For this reason, this method is applicable to the coupling of both electron-deficient and electron-rich aryl bromides. The rate-limiting step could be the β-elimination of the $ArCH_2$-CH(Pd)C*H*(OH)(R) (Scheme 1) and $ArCH_2CH(Pd)$ CMe(OH)(R) (Scheme 2) complexes. The β-elimination to form the enol is faster but not possible with 3-substituted alk-1-en-3-ols. This would explain the slower reactions observed with these substituted alkenols. Both in terms of substrate/catalyst ratio and reaction scope, this catalyst is effective for Heck reactions of alk-1-en-3-ol derivatives. Due to the high price of palladium, the advantage of such low catalyst loading reactions could become increasingly important for industrial processes.

Acknowledgements

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12. As a typical experiment (Table 2, entry 7), the reaction of 4-fluorobromobenzene (1.75 g, 10 mmol), linalool (3.09 g, 20 mmol) and K_2CO_3 (2.76 g, 20 mmol) at 130 °C over 20 h in dry DMF (10 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl) cyclopentane/$[PdCl(C_3H_5)]_2$ complex (0.001 mmol) under argon afforded the corresponding product 1-(4-fluorophenyl)-3,7-dimethyl-octa-1,6-dien-3-ol after evaporation and filtration on silica gel in 81% (2.01 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, 2H, $J = 8.5$ and 5.5 Hz), 6.98 (t, 2H, $J = 8.5$ Hz), 6.55 (d, 1H, $J = 16.1$ Hz), 6.17 (d, 1H, $J = 16.1$ Hz), 5.15 (t, 1H, $J = 6.8$ Hz), 2.15–1.95 (m, 2H), 1.72 (b s, 1H), 1.70–1.65 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (d, $J_{C-F} = 246.1$ Hz), 136.4, 133.2, 132.2, 127.9 (d, $J_{C-F} = 8.0$ Hz), 126.0, 124.3, 115.4 (d, $J_{C-F} = 21.2$ Hz), 73.4, 42.5, 28.4, 25.7, 22.9, 17.7.