Halide-free ethylation of phenol by multifunctional catalysis using phosphinite ligands

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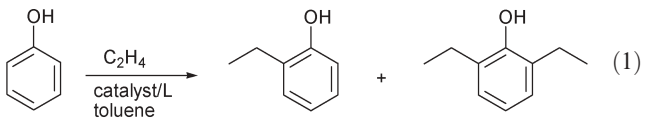
The *ortho*-alkylation of phenols or aniline by catalytic C–H activation and multifunctional catalysis is described.

The formation of carbon–carbon bonds is a key component of many transformations in the pharmaceutical, agrochemical and organic chemical industries. Generally speaking, these transformations involve the reaction of alkyl or aryl halides with an alkyl or arylating agent, or with an alkene (Heck, Suzuki, Stille *etc.* couplings). In all these cases, the halogen is first introduced into one of the substrates and is then lost, necessitating extra synthetic steps and generating waste. Replacing such reactions by the direct replacement of C–H bonds[1] would be a major step towards cleaner more efficient syntheses. The ruthenium-catalysed Murai reaction[2,3] allows the insertion of ethene into an *ortho* C–H bond of acetophenone, but is restricted to ketones because *ortho*-metallation is only favoured if a 5-membered ring is formed. We now report that the Murai reaction can be extended to include substrates such as phenols or anilines by attaching the substrate to phosphorus. After alkylation, the product is released and the new substrate introduced onto P by a transesterification reaction. We have previously used such transesterifications for the hydrogenation of acrylic acids *via* mixed anhydrides with phosphinic acids,[4] whilst Bedford and Limmert have shown that a similar type of reaction can be used for the *ortho*-arylation of phenols by aryl bromides.[5] There has been a report[6] of the stoichiometric alkylation of triphenylphosphite with ethylene, catalysed by ruthenium complexes; weak catalytic activity (15 total turnovers) was observed when the reaction was carried out in the presence of excess phenol and base.



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Reactions between phenol and ethene (30 bar) were carried out at different temperatures (80 to 150 °C) using Wilkinson's catalyst or [RhCl(cyclooctene)$_2$]$_2$ (30 mol%) in the presence of R$_2$P(OPh) (R = Et or Ph). These studies revealed that 120 °C was the best temperature to conduct the reaction. No reaction was observed in the absence of the phosphinite. The coordination of Et$_2$P(OPh) to these metallic precursors was confirmed by NMR experiments, where [RhCl(Et$_2$P(OPh))$_3$] was observed in both cases.†

Results obtained with smaller catalyst loadings are collected in Table 1. High conversions, mainly to 2,6-diethylphenol, are obtained in all cases, with Ph$_2$P(OPh) giving slightly higher yields than Et$_2$P(OPh). We think that this may be because of the very high oxygen sensitivity of Et$_2$P(OPh). GC analysis of the spent reaction solutions showed that all of the phosphinite was oxidised to Et$_2$P(O)(OR) (R = Ph, 2-EtC$_6$H$_4$ or 2,6-Et$_2$C$_6$H$_3$).

Using the [RhCl(cyclooctene)$_2$]$_2$ as the catalyst precursor, the yields are generally lower than with Wilkinson's catalyst under all of the studied conditions. This may be because triphenylphosphine helps to ensure that stable rhodium complexes are present at all times, even if some of the phosphinite is degraded.

A possible reaction mechanism for the alkylation reaction is shown in Scheme 1. After coordination of the phosphinite ligand and *ortho*-metallation, ethene coordinates and hydride migration gives a coordinated ethyl group. Reductive elimination of the ethylated product occurs and transesterification at P with phenol leads to 2-ethylphenol, which can itself enter the catalytic cycle to give diethylphenol. Diethylphenol may also be formed by a second alkylation prior to transesterification.

Given the high efficiency of the rhodium catalysts, we studied the behaviour of other metals (Table 2), although the results were not as good as with rhodium.

With the Pd(II) catalyst, there was no reaction at any temperature studied, although a small amount of activity to give 2-ethylphenol was found when using Pd(0) at 120–150 °C. Since oxidative addition (*ortho*-metallation) is important in the catalytic cycle, a low-valent catalyst precursor is essential. The ruthenium catalyst was more active than the palladium complexes, although the maximum conversion reached was 31.5% at 150 °C. In this case, diethylphenol was produced, but 2-ethylphenol was the main product at all temperatures.

In order to study the versatility of the reaction, we have investigated other substrates for ethylation, such as aniline and cresols. We have tried the reaction using aniline as the substrate, using Wilkinson's catalyst in the presence of Ph$_2$P(NHPh). The results are collected in the Table 3.

With aniline, the result was much less efficient than with phenol. Even with 30% catalyst, the maximum conversion was 27.3% at 150 °C. It is also interesting that in this case, the yields of both products increased with temperature, and that the result at 150 °C was better than at 120 °C. The fact that the yields under these conditions were barely more than stoichiometric may suggest that the transamination step is not occurring. Using lower catalyst loadings (5%), the conversion after 15 h (9.4% 2-ethylaniline, 8.3% 2,6-diethylaniline) could also be accounted-for by reactions not involving transesterification. However, the reaction did not stop, and continued at an increased rate (to give 15.1% 2-ethylaniline and 33.2% diethylaniline), which must have involved some

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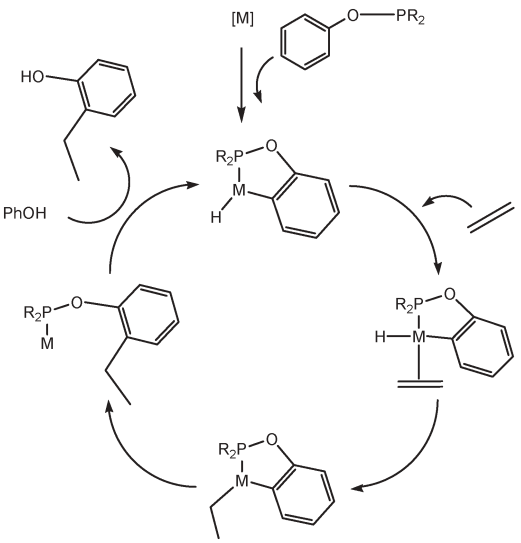
Table 1 Rhodium-catalyzed ethylation of phenol[a]

Entry	Catalyst	Mol% catalyst	Ligand	Yield ethylphenol (%)[b]	Yield diethylphenol (%)[b]
1	$[RhCl(PPh_3)_3]$	5	$Et_2P(OPh)$	10.7	76.3
2	$[RhCl(PPh_3)_3]$	5	$Ph_2P(OPh)$	0.0	87.5
3	$[RhCl(PPh_3)_3]$	2.5	$Ph_2P(OPh)$	0.9	93.1
4	$[RhCl(PPh_3)_3]$	1	$Ph_2P(OPh)$	7.0	19.6
5	$\{RhCl(cyclooct)_2\}_2$	5	$Et_2P(OPh)$	5.7	30.6
6	$\{RhCl(cyclooct)_2\}_2$	5	$Ph_2P(OPh)$	4.3	65.3
7	$\{RhCl(cyclooct)_2\}_2$	2.5	$Ph_2P(OPh)$	5.4	52.4
8	$\{RhCl(cyclooct)_2\}_2$	1	$Ph_2P(OPh)$	3.7	16.2

[a] Reaction conditions: 6 mmol phenol; $P_{ethylene}$ = 30 bar; T = 120 °C; reaction time = 15 h; solvent = 10 ml toluene; catalyst/ligand ratio = 1 : 3.3. [b] Yields were determined from GC, based on the total amount of phenoxide present at the start (including ligand).



Scheme 1 Possible mechanism of the ethylation of phenol by multifunctional catalysis.

transamination. It seems that there is probably an induction period for forming the active catalyst, but that the overall catalytic reaction is very slow.

In the reaction with aniline as the substrate, small amounts of *N*-ethylaniline and 2-methylquinoline were formed; however, they are sub-stoichiometric. We have also observed 2-ethylphenyldiphenylphosphine from the ethylation of PPh_3 in reactions involving Wilkinson's catalyst.

To study the possible effect of the methyl group in different positions on the phenol ring, the reaction has also been investigated using Wilkinson's catalyst and different cresols . The ligands were synthesized by the same procedure as the phenol-derived ligand, using the corresponding cresol in each case.‡

When the reaction was run with the $Ph_2P(OPh)$ ligand, the result was similar to that obtained with a ligand derived from the relevant cresol, but a mixture of ethyl and diethylphenol, and ethyl and diethylcresol (when possible) was observed. Because of this, each cresol-derived ligand was synthesized to facilitate analysis of the results by GC. The results are summarized in Table 4.

Table 2 Catalytic ethylation of phenol[a]

Entry	Catalyst	T/°C	Ligand	Yield ethylphenol (%)[b]	Yield diethylphenol (%)[b]
1	$[PdCl_2(CH_3CN)_2]$	80	$Et_2P(OPh)$	—	—
2	$[PdCl_2(CH_3CN)_2]$	120	$Et_2P(OPh)$	—	—
3	$[PdCl_2(CH_3CN)_2]$	150	$Et_2P(OPh)$	—	—
4	$[Pd_2(dba)_3]$	80	$Ph_2P(OPh)$	—	—
5	$[Pd_2(dba)_3]$	120	$Ph_2P(OPh)$	4.5	—
6	$[Pd_2(dba)_3]$	150	$Ph_2P(OPh)$	5.6	—
7	$[RuH_2(CO)(PPh_3)_3]$	80	$Ph_2P(OPh)$	11.3	7.5
8	$[RuH_2(CO)(PPh_3)_3]$	120	$Ph_2P(OPh)$	14.0	8.9
9	$[RuH_2(CO)(PPh_3)_3]$	150	$Ph_2P(OPh)$	17.2	14.3

[a] Reaction conditions: 1 mmol phenol; 0.3 mmol catalyst; $P_{ethylene}$ = 30 bar; reaction time = 15 h; solvent = 10 ml toluene; catalyst/ligand ratio = 1 : 3.3. [b] Yields were determined from GC.

Table 3 Rhodium catalyzed ethylation of aniline[a]

Entry	Aniline/mmol	Mol% catalyst	T/°C	Ligand	Yield ethylaniline (%)[b]	Yield diethylaniline (%)[b]
1	1	30	80	$Ph_2P(NHPh)$	4.9	3.6
2	1	30	120	$Ph_2P(NHPh)$	6.8	5.9
3	1	30	150	$Ph_2P(NHPh)$	17.1	10.2
4	6	5	120	$Ph_2P(NHPh)$	3.2	0.7
5	6	5	150	$Ph_2P(NHPh)$	9.4	8.3
6[c]	6	5	150	$Ph_2P(NHPh)$	15.1	33.2

[a] Reaction conditions: 3 mmol $RhCl(PPh_3)_3$ catalyst; $P_{ethylene}$ = 30 bar; reaction time = 15 h; solvent = 10 ml toluene; catalyst/ligand ratio = 1 : 3.3. [b] Yields were determined from GC. [c] Reaction time = 25 h.

Table 4 Rhodium-catalyzed ethylation of different cresols[a]

Entry	Mol% catalyst	Ligand	Yield ethylcresol (%)[b]	Yield diethylcresol (%)[b]
1	5	$Ph_2P(OPh)$	0.7	99.1
2	5	$Ph_2P(O(p\text{-}MeC_6H_4))$	1.6	98.1
3	2.5	$Ph_2P(O(p\text{-}MeC_6H_4))$	5.0	89.0
4	1	$Ph_2P(O(p\text{-}MeC_6H_4))$	5.8	51.6
5	5	$Ph_2P(OPh)$	44.6	55.4
6	5	$Ph_2P(O(m\text{-}MeC_6H_4))$	44.1	55.9
7	2.5	$Ph_2P(O(m\text{-}MeC_6H_4))$	69.5	30.5
8	1	$Ph_2P(O(m\text{-}MeC_6H_4))$	84.4	1.3
9	5	$Ph_2P(OPh)$	98.9	—
10	5	$Ph_2P(O(o\text{-}MeC_6H_4))$	88.9	—
11	2.5	$Ph_2P(O(o\text{-}MeC_6H_4))$	69.1	—
12	1	$Ph_2P(O(o\text{-}MeC_6H_4))$	22.3	—

[a] Reaction conditions: 6 mmol cresol; $RhCl(PPh_3)_3$ catalyst; $P_{ethylene}$ = 30 bar; T = 120 °C; reaction time = 15 h; solvent = 10 ml toluene; catalyst/ligand ratio = 1 : 3.3. [b] Yields were determined from GC, based on the ratio of the integration of each product in the corresponding FID chromatogram.

For *para*-cresol, it seems that the methyl group does not impart any steric hindrance, and the results are comparable to those obtained with phenol. Under all conditions, diethylcresol was the main product of the reaction. With 5% catalyst, the conversion was almost total to the diethylated product, and the yield was only slightly lower with 2.5% catalyst. However, with 1% catalyst, the yield was, as with phenol, significantly reduced.

For *meta*-cresol, the second ethylation is much more difficult because the 2-position of the phenyl ring is less accessible due to the nearby methyl group. This means that with 5% catalyst, the selectivity for the diethylated product was only 55.9%, while the rest was only monoethylated. As the amount of catalyst was decreased, the ratio of ethylated/diethylated product increased, and with 1% catalyst (Table 4, entry 8), the first ethylation was almost complete before the second ethylation had started.

For *ortho*-cresol, no C–H activation of the methyl group occurred, and only ethylation in the other *ortho* position was observed. Thus, this ligand gives the worst activity results, and the result was only slightly better when the diphenyl ligand was used (Table 4, entry 9) than when the ligand with *ortho*-cresol was used (Table 4, entry 10). Therefore, it seems than the *ortho*-cresol may impart some steric hindrance around the rhodium centre, which could inhibit the *ortho*-metallation step.

In summary, we have developed a system for the ethylation of different aromatic compounds by multifunctional catalysis based on rhodium complexes of R_2PXPh ligands (R = Ph or Et, X = O or NH) that involves C–H activation and 100% atom economy.

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Notes and references

† The reaction needed 2 h for completion when using Wilkinson's catalyst, and only 0.5 h when the dimer was used. $[RhCl(Et_2P(OPh))_3]$, ^{31}P NMR (C_6D_6): δ = 155.6 (dd, 2 P, $^1J_{P-Rh}$ = 158.3 Hz, $^2J_{P-P}$ = 37.8 Hz) and 161.7 (dt, 1 P, $^1J_{P-Rh}$ = 206.1 Hz, $^2J_{P-P}$ = 37.7 Hz).
‡ ^{31}P NMR (C_6D_6): δ = 112.7 ($Ph_2P(O(p\text{-}MeC_6H_4))$), 111.7 ($Ph_2P(O(m\text{-}MeC_6H_4))$) and 111.5 ($Ph_2P(O(o\text{-}MeC_6H_4))$).

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