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C–C Bond formation from alcohols using a Xantphos ruthenium complex

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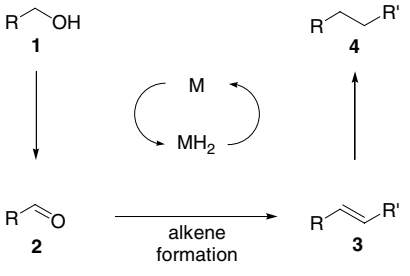
Abstract—A ruthenium complex of Xantphos has been shown to be a good catalyst for the alkylation of active methylene compounds with a range of alcohols.

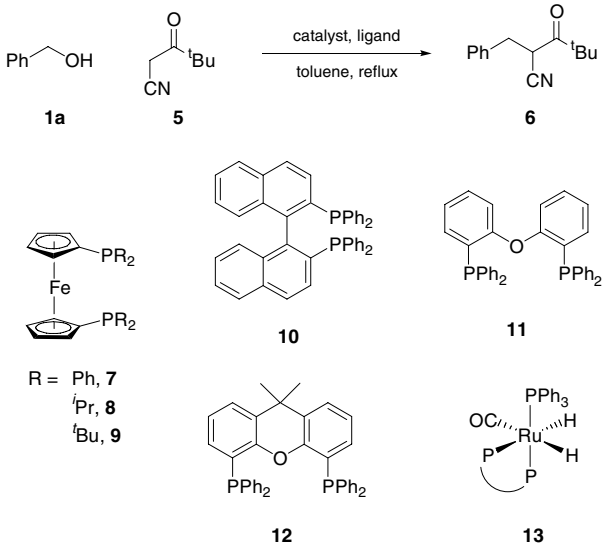
The alkylation of activated methylene compounds is commonly carried out with alkyl halides. Due to the toxic and often mutagenic properties of these alkyl halides, an attractive alternative is to use alcohols as alkylating agents. We have recently demonstrated that iridium[1] and ruthenium[2] catalysts can be used for the formation of C–C bonds from alcohols via an indirect Wittig reaction. In this chemistry, the metal catalyst borrows hydrogen from the alcohol substrate **1**, temporarily forming an intermediate aldehyde **2**, which undergoes a transformation into alkene **3**. The borrowed hydrogen is then returned to the alkene to form the new C–C bond in product **4**, as shown in Scheme 1.

The conversion of the intermediate aldehyde into the intermediate alkene can be achieved using methods other than Wittig olefination. For example, we have achieved an iridium catalysed alkylation of alcohols using malonates and nitroalkanes.[3] Other researchers have alkylated nitriles[4,5] and ketones[6–8] using a similar 'borrowing hydrogen' strategy although there is often a need for long reaction times, high catalyst loading, or an excess of one of the coupling partners. We were interested to find catalysts that would allow this approach to C–C bond-forming reactions to occur more readily, and would avoid the formation of triphenylphosphine oxide from the indirect Wittig chemistry.



Scheme 1. Borrowing hydrogen in the alkylation of alcohols.

We identified the reaction between benzyl alcohol **1a** and ketonitrile **5** as a model reaction for an oxidation-Knoevenagel-reduction process to provide alkylated product **6** (Scheme 2). As expected, the iridium catalysed



Scheme 2. Reaction of benzyl alcohol **1a** with ketonitrile **5**.

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Table 1. Comparison of ligands for C–C bond formation[a]

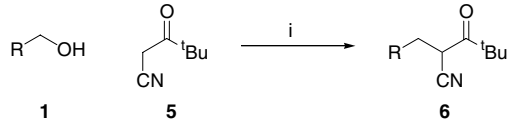
Entry	Metal (loading, mol %)	Ligand	Time (h)	Conversion (%)
1[b]	Ir (5)	**7**	24	55
2	Ru (5)	—	18	56
3	Ru (0.5)	**7**	3	56
4	Ru (0.5)	**8**	3	91
5	Ru (0.5)	**9**	16	<1
6	Ru (0.5)	**10**	16	22
7	Ru (0.5)	**11**	3	8
8	Ru (0.5)	**12**	3	100

[a] Typical reaction conditions: Benzyl alcohol **1a** (1 equiv), ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), ligand (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux.
[b] $[Ir(cod)Cl]_2$ (2.5 mol %), dppf **7** (5 mol %), K_2CO_3 (5 mol %), 3 Å molecular sieves, piperidinium acetate (25 mol %), PhMe, reflux.

process that we had previously explored required high catalyst loadings and long reaction times to achieve a successful reaction (Table 1, entry 1). Variation of the ligand with the iridium catalyst did not lead to any improvement, and our attention turned to the use of ruthenium-based complexes.

Whilst the use of $Ru(PPh_3)_3(CO)H_2$ offered no clear improvement, we were pleased to find that the use of dppf **7** as an additive provided a significantly more reactive catalytic system. The more electron rich ferrocene-based ligand **8** offered further improvement, but when the *tert*-butyl analogue **9** was employed, the reaction was very slow, presumably due to the steric requirements of this ligand. Application of other bidentate ligands in this process identified the ligand Xantphos **12** as an excellent choice for this reaction, and allowed the alkylation process to occur within 3 h using only 0.5 mol % of catalyst. Ligand **12** has been shown to enhance the reactivity of several transition metal catalysed reactions,[9,10] and is known to provide a wide bite angle upon complexation. The addition of more than 1 equiv of **12** to $Ru(PPh_3)_3(CO)H_2$ provided only a small benefit; 93% conversion was observed after 30 min using 1 equiv of ligand, whilst 98% conversion was obtained using 2 equiv of ligand under otherwise identical conditions. Ruthenium complex **13** was prepared by exchange of phosphine ligands,[11] and this pre-formed catalyst gave 99% conversion in 30 min.

Murahashi has reported that some ruthenium complexes catalyse the condensation of activated nitriles with aldehydes,[12] but in these reactions we found that piperidinium acetate was needed to catalyse the condensation. Other amines or ammonium acetates were found to be inferior.[13]



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Scheme 3. Alkylation of other alcohols with ketonitrile **5**. Reagents and conditions: (i) $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), Xantphos **12** (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux, 4 h.

Table 2. C–C bond formation using the Ru/Xantphos catalyst[a]

Entry	Alcohol	Conversion (%)	Yield (%)
1	$PhCH_2OH$, **1a**	100	78
2	*p*-$MeOC_6H_4CH_2OH$, **1b**	100	83
3	*p*-$FC_6H_4CH_2OH$, **1c**	100	89
4	*p*-$F_3CC_6H_4CH_2OH$, **1d**	100	83
5	*p*-$O_2NC_6H_4CH_2OH$, **1e**	52	31
6	*p*-$BrC_6H_4CH_2OH$, **1f**	100	79
7	*o*-$MeOC_6H_4CH_2OH$, **1g**	100	82
8	Furfuryl alcohol, **1h**	11	Not isolated

[a] Typical reaction conditions: Alcohol (1 equiv), ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), ligand (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux, 4 h.

We chose to use 1 equiv of ligand with in situ generation of catalyst as a convenient procedure for examining the alkylation of other alcohols (Scheme 3). For benzylic alcohols **1a–g**, we allowed the reactions to run for 4 h, to ensure complete reaction. As shown in Table 2, all benzylic alcohols were fully converted into product with the exception of *p*-nitrobenzyl alcohol **1e** and furfuryl alcohol **1h** (entries 5 and 8, respectively). The oxidation of *p*-nitrobenzyl alcohol **1e** is retarded by the presence of the electron-withdrawing nitro group, and we speculate that the furyl ring may inhibit catalysis by chelation.

We were pleased to find that this system could be applied to aliphatic alcohols (Table 3). Complete conversion was achieved in 4 h, although a higher catalyst loading was required, presumably due to the difficult nature of these oxidations. Whilst 5 mol % catalyst was routinely used, in the case of 2-phenylethanol we have shown that complete conversion is still obtained with a lower catalyst loading of 2.5 mol % (entry 3).

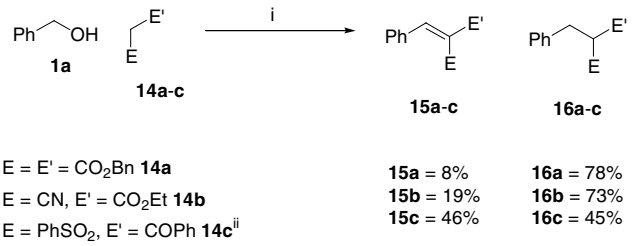
Other nucleophiles were examined for the alkylation of benzyl alcohol (Scheme 4). Dibenzyl malonate **14a** and cyano ester **14b** were alkylated in reasonable yields, but required longer reaction times. Sulfone **14c** afforded product **16c** along with the intermediate alkene **15c**, which had not been hydrogenated. We[14] and others[15] have previously reported that alcohols can be oxidised by a loss of H_2, and this may explain the oxidation observed here.

In summary, we have shown that the use of alcohols as alkylating agents provides an attractive alternative to conventional, often toxic, alkyl halides. Ketonitrile **5** has been alkylated with a range of alcohols giving excel-

Table 3. C–C bond formation using aliphatic alcohols[a]

Entry	Alcohol	Conversion (%)	Yield (%)
1	Furfuryl alcohol, **1h**	100	72
2	$PhCH_2CH_2OH$, **1i**	100	—
3[b]	$PhCH_2CH_2OH$, **1i**	100	87
4	Undecanol, **1j**	100	85
5	Cyclopropyl methanol, **1k**	100	69
6	Tryptophol, **1l**	100	76

[a] Typical reaction conditions: Alcohol (1 equiv) and ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (5 mol %), ligand (5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.
[b] $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %), ligand (2.5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.



Scheme 4. Use of other active methylene compounds in C–C bond formation. Reagents and conditions: (i) $Ru(PPh_3)_3(CO)H_2$ (5 mol %), Xantphos **12** (5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 24 h. (ii) $Ru(PPh_3)_3(CO)H_2$ (2 mol %), Xantphos **12** (2 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.

lent conversions with catalyst loadings as low as 0.5 mol % Ru. The incorporation of the rigid bidentate phosphine Xantphos **12** has a remarkable ligand acceleration effect and proves crucial to the high reactivity of the ruthenium catalyst. Good to excellent conversions have also been achieved for the alkylation of a selection of activated methylene compounds.

Acknowledgments

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