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# C–C bond formation from alcohols and malonate half esters using borrowing hydrogen methodology

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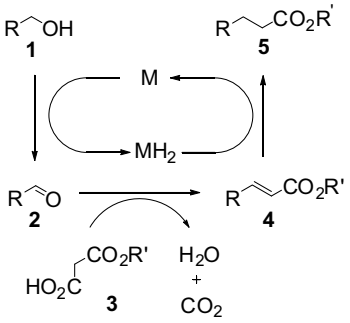
ABSTRACT

Alcohols have been used as alkylating agents in a decarboxylative reaction with malonate half esters via a borrowing hydrogen pathway catalysed by readily available $Ru(PPh_3)_3Cl_2$.



Alcohols are generally poor electrophiles for alkylation reactions, requiring activation of the hydroxyl into a suitable leaving group in order to facilitate nucleophilic substitution.[1] An alternative strategy for alcohol activation involves the removal of hydrogen from the alcohol to form an aldehyde, which undergoes in situ conversion into an alkene prior to return of hydrogen to afford a net alkylation process. We have termed this oxidation/alkene-formation/reduction sequence 'borrowing hydrogen' methodology.[2–4] Alkylation reactions of alcohols proceeding by this mechanism have been achieved using ketones,[5] nitriles[6] and nitroalkanes[7] as the readily deprotonated carbon nucleophiles. However, the use of simple esters has not been reported for these reactions and the conversion of ROH into $RCH_2CO_2R'$ has only been achieved using Wittig reagents as the alkene-forming reagent.[8] We therefore considered the use of malonate half esters as convenient reagents for alkylation reactions according to the pathway outlined in Scheme 1.

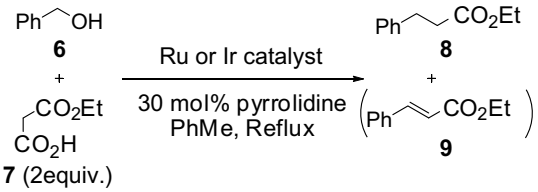
Temporary removal of hydrogen from alcohol **1** was expected to generate the aldehyde **2** which would undergo a decarboxylative Knoevenagel reaction with malonate half ester **3** giving the α,β-unsaturated ester **4**. Return of the hydrogen by alkene reduction would then provide the overall alkylation product **5**. The decarboxylative Knoevenagel reaction of aldehydes is a well-known process, which is usually catalysed by a suitable amine.[9] Since the only by-products formed in the decarboxylative Knoevenagel reaction are water and carbon dioxide, this process provides a useful alternative to the Wittig reaction for the conversion of aldehydes into α,β-unsaturated esters.[10]




**Scheme 1.** Strategy for alkylation of alcohols with malonate half esters.

As a model system, we chose to investigate the reaction of benzyl alcohol **6** with monoethyl malonate **7** to prepare ethyldihydrocinnamate **8** (Scheme 2). Pyrrolidine was chosen as the organocatalyst based on its known ability to effect the decarboxylative Knoevenagel reaction.[9] For the transition metal at the heart of the borrowing hydrogen chemistry, we investigated (i) $Ru(PPh_3)_3(CO)H_2$/xantphos[11] which we had previously found to be useful in hydrogen transfer reactions,[12] (ii) $Ru(PPh_3)_3Cl_2$/KOH as a cheap, readily available Ru(II) source[13] and (iii) $[Cp^*IrCl_2]_2/Cs_2CO_3$ as used by Fujita and Yamaguchi for a good effect in C–C and C–N bond-forming reactions from alcohols.[14] A summary of these trial reactions is given in Table 1.

All of the catalysts examined were successful for the conversion of benzyl alcohol **6** into the alkylated product **8**, although both of the ruthenium catalysts also gave significant amounts of alkene by-product **9**. We assume that not all of the alkene was reduced because of hydrogen loss, probably as $H_2$ gas.[15] When a suitable hydrogen acceptor was added, it was possible to generate alkene




**Scheme 2.** Catalyst identification for the alkylation of benzyl alcohol.

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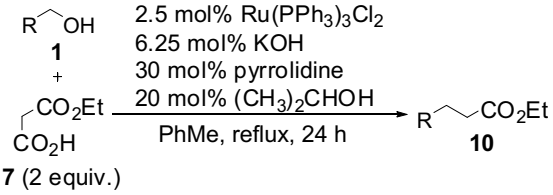
**Table 1**
Formation of ester **8** from alcohol **6**

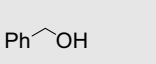
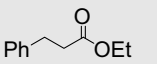
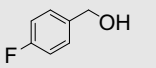
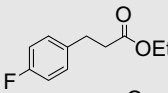
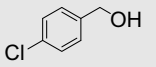
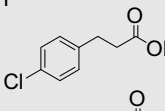
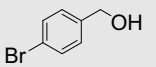
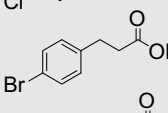
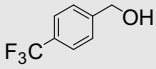
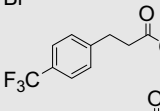
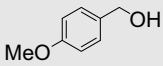
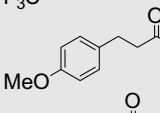
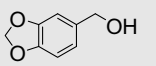
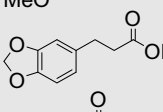
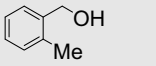
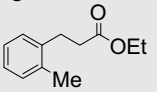
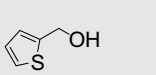
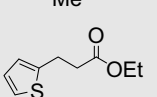
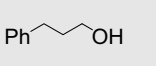
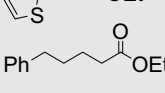
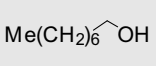
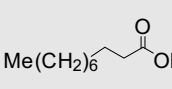
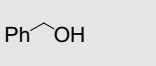
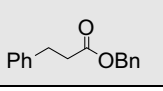
| Catalyst[a] | Conv.[b] (%) | Time (h) | **8**:**9** C–C:C=C |
|---|---|---|---|
| $Ru(PPh_3)_3(CO)H_2$/xantphos | 100 | 24 | 62:38 |
| $Ru(PPh_3)_3Cl_2$/KOH | 100 | 24 | 92:8 |
| $Ru(PPh_3)_3Cl_2$/KOH | 93 | 4 | 82:11 |
| $[Cp^*IrCl_2]/Cs_2CO_3$ | 100 | 24 | 100:0 |
| $[Cp^*IrCl_2]/Cs_2CO_3$ | 79 | 4 | 76:3 |

[a] Catalyst loading was 2.5 mol % (i.e., 2.5 mol % in Ru or 5 mol % in Ir).
[b] Conversion was established by analysis of the $^1H$ NMR spectrum.




**Scheme 3.** Reaction conditions used for the conversion of alcohols into doubly homologated esters.

**Table 2**
Conversion of alcohols into doubly homologated ethyl esters

| Entry | Alcohol | Ethyl ester | Yield[a] (%) |
|---|---|---|---|
| 1 |  |  | 88 |
| 2 |  |  | 81 |
| 3 |  |  | 82 |
| 4 |  |  | 72 |
| 5 |  |  | 80[b] |
| 6 |  |  | 72 |
| 7 |  |  | 71 |
| 8 |  |  | 86 |
| 9 |  |  | 73[b] |
| 10 |  |  | 77[b] |
| 11 |  |  | 75[b] |
| 12 |  |  | 100[c] |

[a] Isolated yield after purification by column chromatography, except where stated.
[b] 5 mol % $Ru(PPh_3)_3Cl_2$ and 12.5 mol % KOH were used in these examples.
[c] The product was formed with 100% conversion of alcohol using monobenzylmalonic ester but also contained benzyl acetate (resulting from decarboxylation of the starting material).

**9** as the exclusive reaction product.[16] A comparison of the conversion achieved after 4 h using the $Ru(PPh_3)_3Cl_2$/KOH and $[Cp^*IrCl_2]_2$/$Cs_2CO_3$ catalysts revealed that the ruthenium catalyst was slightly more effective for this process. In combination with the fact that the effective catalyst loading was lower for the Ru catalyst than the Ir catalyst (where 2.5 mol % dimer = 5 mol % Ir) and the relative costs of these complexes, we chose to develop further the scope of the $Ru(PPh_3)_3Cl_2$/KOH catalyst. In order to overcome the problem of unreacted alkene, we added isopropanol (20 mol %) which acts as a hydrogen donor to replace any lost $H_2$. Therefore, under the reaction conditions identified in Scheme 3, a range of alcohols **1** was converted into the doubly homologated esters **10** (Table 2).[17,18]

The reaction proved to be successful for a range of benzylic alcohols (entries 1–9), including the *p*-fluoro, *p*-chloro- and *p*-bromo-substituted alcohols in entries 2–4. Electron-rich benzylic alcohols (entries 6 and 7) and a heterocyclic example (entry 9) were also successful. However, the electron-deficient *p*-trifluoromethyl-substituted benzylic alcohol (entry 5) and aliphatic alcohols were less reactive and required a higher catalyst loading to reach completion under these conditions. The lower reactivity of these alcohols parallels the expected ease of oxidation for these substrates.

The same reaction conditions were employed using monobenzylmalonic ester to give the benzyl ester product in entry 12. Whilst the product was still formed with 100% conversion, it was contaminated with involatile benzyl acetate, presumably formed by decarboxylation of the starting monoester.

In summary, alcohols have been successfully converted into doubly homologated esters using borrowing hydrogen methodology and malonate half esters, which undergo a decarboxylative Knoevenagel reaction on the intermediate aldehyde.

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17. *Procedure for the synthesis of ethyl dihydrocinnamate* (Table 1, *entry 1*): To an oven-dried, argon-purged Radley's carousel tube containing $Ru(PPh_3)_3Cl_2$ (96 mg, 0.1 mmol, 0.025 equiv), KOH (14.4 mg, 0.25 mmol, 0.0625 equiv) and pyrrolidine (100 μL, 1.2 mmol, 0.30 equiv) were added toluene (4 mL), benzyl alcohol (436 μL, 4 mmol, 1 equiv), isopropanol (60.8 μL, 0.8 mmol, 0.20 equiv) and monoethyl malonate (944 μL, 8 mmol, 2 equiv). The reaction mixture was heated to reflux for 24 h with a constant flow of argon, cooled to room temperature and the solvent was removed in vacuo. The resultant oil was purified by column chromatography (9:1 petroleum ether (bp 40–60 °C)/diethyl ether, $R_f = 0.31$) affording the product as a colourless oil (627 mg, 88%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32–7.23 (m, 5H), 4.15 (q, 2H, $J = 7.2$ Hz), 2.99 (t, 2H, $J = 8.1$ Hz), 2.64 (t, 2 H, $J = 8.1$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 173.3, 141.0, 130.6, 128.9, 126.6, 60.9, 36.3, 31.4, 14.6.
18. *Procedure for the synthesis of ethyl 3-(2-thienyl)-propanoate (*Table 1, *entry 9):* To an oven-dried, argon-purged Radley's carousel tube containing $Ru(PPh_3)_3Cl_2$ (192 mg, 0.2 mmol, 0.05 equiv), KOH (28.8 mg, 0.125 mmol, 0.125 equiv) and pyrrolidine (100 μL, 1.2 mmol, 0.30 equiv) were added toluene (4 mL), 2-thiophenemethanol (378 μL, 4 mmol, 1 equiv), isopropanol (60.8 μL, 0.8 mmol, 0.20 equiv) and monoethyl malonate (944 μL, 8 mmol, 2 equiv). The reaction mixture was heated to reflux for 24 h with a constant flow of argon, cooled to room temperature and the solvent was removed in vacuo. The resultant oil was purified by column chromatography (19:1 petroleum ether (bp 40–60 °C)/EtOAc $R_f = 0.62$) affording the product as a colourless oil (534 mg, 73%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.11 (dd, 1H, $J = 1.2$ Hz, 5.1 Hz), 6.91 (dd, 1H, $J = 3.3$ Hz, 5.1 Hz), 6.82 (m, 1H), 4.15 (q, 2H, $J = 7.2$ Hz), 3.17 (t, 2H, $J = 7.5$ Hz), 2.67 (t, 2H, $J = 7.5$ Hz), 1.23 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 172.7, 143.5, 127.2, 125.1, 123.9, 60.8. 36.5, 25.5, 14.6.