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# sp$^3$C–H bond alkylation of ketones with alkenes *via* ruthenium(II) catalysed dehydrogenation of alcohols†

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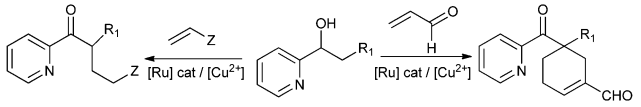
**The sp$^3$C–H bond functionalisation of 2-pyridyl ethanols upon reaction with alkenes, in the presence of a [RuCl$_2$(arene)]$_2$ catalyst and Cu(OAc)$_2$·H$_2$O, is performed under mild conditions without additional base. This reaction proceeds *via* a tandem alcohol dehydrogenation/alkylation with alkenes of the resulting ketone at its α sp$^3$C–H bond.**

The functionalisation of sp$^3$C–H bonds attracts interest in the development of new synthetic methods and the fast building of polyfunctional molecules,[1] the easy modification of ligands or the preparation of molecular luminescent and photochromic materials.[2] The direct catalytic functionalisation of sp$^3$C–H bond *via* arylation at the α position of the carbonyl of a ketone has been shown to be promoted by palladium catalysts with strong base to generate the enolate intermediate:[1,3] the Pd(0)/diphosphine catalysed α-arylation of ketones with aryl bromides has been initially performed by Buchwald[4] in the presence of NaOt-Bu, and by Hartwig[5] using KN(SiMe$_3$)$_2$ as a base. However, recently, Lam reported a ruthenium-catalysed oxidative annulation of 2-aryl-1,3-dicarbonyl compounds with alkynes into spiroindenes *via* an easily generated enolate species.[6]

To the best of our knowledge, the ruthenium(II) functionalisation of sp$^3$C–H bond at the β position of alcohols, by alkylation with alkenes, has not been reported yet, in spite of the well-established hydrogen borrowing reactions especially using Ru(II) catalysts that are able to dehydrogenate alcohols *via* hydrido-ruthenium species formation.[7] In the latter reactions generating aldehyde, alkylation can take place but *via* aldol condensation/hydrogenation.[7g–j] We thus became interested in investigating the consecutive catalytic alcohol dehydrogenation and neighbouring sp$^3$C–H or sp$^2$C–H bond functionalisation. As the C–H bond activation step by Ru(II) catalysts often requires a coordinating directing group,[8] we first considered the activation of coordinating 2-pyridyl alcohols, as some of their derivatives are bioactive,[9,10] or constitute a class of useful *N*,*O*-bidentate ligands in 5-membered cyclic metal complexes.[11]



Scheme 1 Ru(II) catalysed dehydrogenation of 2-pyridyl alcohol and tandem alkylation/condensation of 2-pyridyl ketone.

Here we report the Ru(II) catalysed dehydrogenation of 2-pyridyl alcohols in the presence of Cu(OAc)$_2$·H$_2$O and the subsequent alkylation at the α position of the resulting ketones with alkenes, and with acrolein, the double alkylation and intramolecular aldol condensation, formally *via* sp$^3$C–H bond functionalisation. We also show that the 2-pyridyl ketone can be alkylated with alkene at the α-position of the carbonyl using only Ru(OAc)$_2$(*p*-cymene) catalyst but in the presence of isopropanol (Scheme 1).

In an attempt to perform the competitive Ru(II) catalysed alcohol dehydrogenation *versus* oxidative dehydrogenative alkenylation of the phenyl group[12] of the *N*-coordinating benzyl 2-pyridyl alcohol **1a** with methyl acrylate **2a**, we first studied the action of [RuCl$_2$(*p*-cymene)]$_2$ as a pre-catalyst in the presence of carboxylates, and Cu(OAc)$_2$·H$_2$O (1 equiv.) at 120 °C for 20 h, which surprisingly led to the formation of α-alkylated ketone **3a** (entries 1–2). Interestingly, in the absence of an additive, **3a** was produced in 53% yield (entry 3 and Table S1, ESI†). The reaction thus required the presence of both [RuCl$_2$(*p*-cymene)]$_2$ and Cu(OAc)$_2$·H$_2$O (entries 4 and 5). Good results were obtained using only 0.8 equiv. of Cu(OAc)$_2$·H$_2$O without air (entries 6 and 7 and Table S2, ESI†). Further experiments show that an excess of **2a** (4 equiv.) (entries 7 and 9) and a slight increase of the ruthenium loading (7.5 mol%) (entry 10) improve the reaction conversion up to 75%. It was found preferable to use only 5 mol% of ruthenium catalyst for 36 h at 120 °C in 1,2-dichloroethane (DCE) to reach 80% conversion and obtain **3a** in a 68% isolated yield (entries 11 and 12). Using Ru(OAc)$_2$(*p*-cymene) as the catalyst is also moderately operative with Cu(OAc)$_2$·H$_2$O (entry 13) (Table S3, ESI†).

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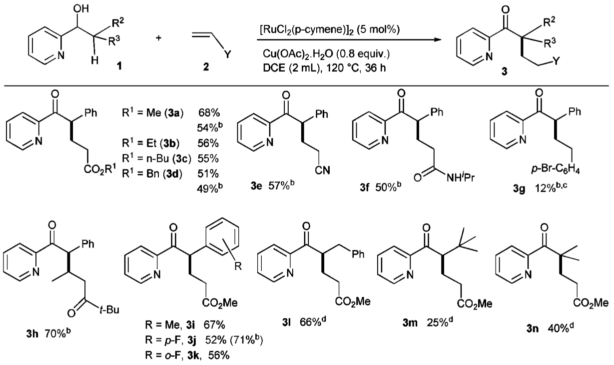
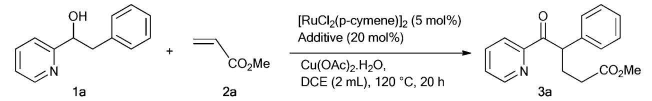


$^a$**1** (0.5 mmol), **2** (2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (0.8 equiv.), DCE (2 mL), 120 °C, 36 h. $^b$Toluene, 150 °C, 20 h. $^c$Detected by GC. $^d$Toluene, 150 °C, 36 h.

Scheme 2 Ruthenium(II) catalysed $sp^3$C–H alkylation of 2-pyridyl methanol derivatives with alkenes.

Table 1 Ruthenium(II)-catalysed $sp^3$ C–H bond alkylation of benzyl 2-pyridyl methanol **1a** with methyl acrylate **2a**$^a$



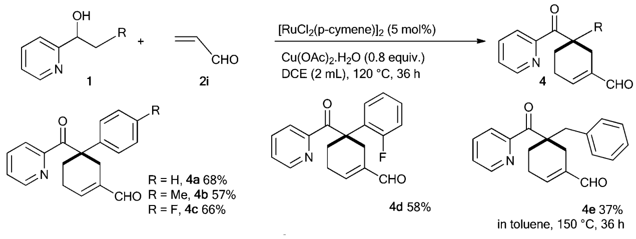
| Entry | **2a** (equiv.) | Additive | $Cu(OAc)_2{\cdot}H_2O$ (equiv.) | Conv.$^b$ (%) |
|---|---|---|---|---|
| 1 | 2 | $C_6H_5CO_2H$ (20 mol%) | 1 | 52 |
| 2 | 2 | $C_6H_5CO_2K$ (20 mol%) | 1 | 57 |
| 3 | 2 | — | 1 | 53 |
| 4 | 2 | — | 0 | —$^i$ |
| 5 | 2 | — (no Ru catalyst)$^c$ | 1 | —$^i$ |
| 6 | 2 | — | 0.8 | 56 |
| 7 | 4 | — | 0.8 | 69(46) |
| $8^d$ | 4 | — | 0.8 | 9 |
| 9 | 6 | — | 0.8 | 72 |
| $10^e$ | 4 | — | 0.8 | 75 |
| $11^f$ | 4 | — | 0.8 | 80(68) |
| $12^g$ | 4 | — | 0.8 | 74(54) |
| $13^h$ | 4 | — | 0.8 | 60 |

$^a$ **1a** (0.25 mmol), **2a** (2–6 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), additive (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.8–1 equiv.), DCE (2 mL), 120 °C, 20 h. $^b$ Detected by GC, in parentheses, isolated yields of **3a**. $^c$ Without Ru catalyst. $^d$ Under air. $^e$ 7.5 mol% of $[RuCl_2(p\text{-cymene})]_2$. $^f$ Run in 0.5 mmol scale, 36 h. $^g$ In toluene, 150 °C. $^h$ 10 mol% of $[Ru(OAc)_2(p\text{-cymene})]$ was used. $^i$ Less than 5% of ketone 2-$PyCOCH_2Ph$ was formed.

We first explore the scope of the reaction with **1a** (Scheme 2) without addition of another base than the $Cu(OAc)_2$ released acetate.

Using the optimised conditions (Table 1, entry 11), the influence of various activated alkenes was explored. In reaction of **1a** with various acrylates **2a–2d**, the alkylated ketones **3a–3d** were obtained in 51–68% isolated yields. The same reaction took place easily with acrylonitrile **2e** and *N*-isopropyl-acrylamide **2f** to give **3e** (57%) and **3f** (50%). The reaction with *p*-bromostyrene, led to a small amount of **3g** (12%) showing that electrophilic alkenes are more efficient. It is noteworthy that the reaction of **1a** with the unsaturated ketone containing a disubstituted C=C bond $CH_3CH{=}CHCOt\text{-}Bu$ **2h**, regioselectively affords the alkylated ketone **3h** in 70% yield.

The reaction of aryl substituted derivatives **1b–d** was then performed under similar conditions. It led to ketones **3i–k** in 52–70% yields. The reaction was then extended to pyridyl alcohols, having a benzyl group **1e** ($R^2$ = Bn, $R^3$ = H) or alkyl groups **1f** ($R^2$ = *t*-Bu, $R^3$ = H) and **1g** ($R^2$ = $R^3$ = Me) linked at the α position of the hydroxyl group, and they afforded the derivatives **3l**, **3m** and **3n**, respectively in 25–66% yields.

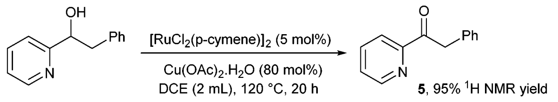


Scheme 3 Ru(II)-catalysed $sp^3$ C–H alkylation of 2-pyridyl ethanol derivatives with acrolein.

The reaction of **1a** with 4 equiv. of acrolein under similar conditions selectively led to the dicarbonyl cyclic derivative **4a** in a 68% isolated yield (Scheme 3). This compound **4a** results formally from a double Michael addition to acrolein of the enolate of ketone **5**, arising from oxidation of **1a**, followed by cyclisation *via* intramolecular aldol condensation. The ketone **5** under the same conditions does not lead to the formation of compound **4**.

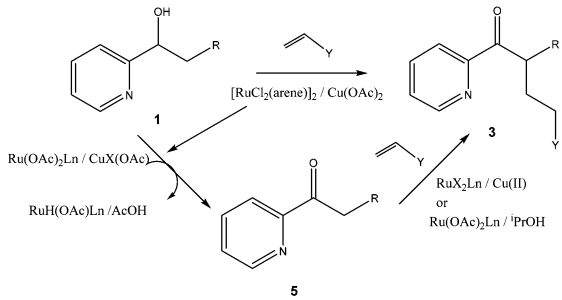
Analogously, the aryl substituted derivatives **4b–d** were obtained in 57–66% yields from the alcohols **1b–d**. The alcohol **1e** (R = Bn) similarly led to the derivative **4e** in 37% yield, resulting from C–C bond formations at the α carbon of the ketone, rather than at the benzylic carbon. This reaction gives a straightforward access to functional 2-pyridyl ketones containing a conjugated formyl cyclohexene moiety.

The above reaction constitutes a straightforward way to perform an alkylation at the α position of a coordinating ketone starting from its alcohol. The conditions and results suggest that the formation of **3** initially involves the dehydrogenation of the alcohol **1** which generates a new active ruthenium species, followed by a formal Michael addition of the enolate to the alkene. First, we showed that only in the presence of *both* $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2{\cdot}H_2O$, the alcohol **1a** was transformed into the (2-pyridyl)benzyl ketone **5** (eqn (1)) (see also ESI,† Scheme S2).



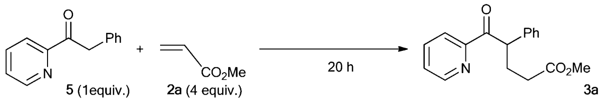
(1)

The alkylation of the ketone **5** with methyl acrylate **2a** was then attempted: by action of both $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) and $Cu(OAc)_2$ (0.8 equiv.), but in the presence of i-PrOH (2 equiv.), the alkylated ketone **3a** was obtained in only 10% GC-yield (eqn (2)). However, when this reaction was performed in the presence of 10 mol% of $Ru(OAc)_2(p\text{-cymene})$ in i-PrOH at 100 °C *without addition of* $Cu(OAc)_2$, **3a** was obtained in 56% GC-yield. However, in DCE instead of isopropanol the alcohol **1f** ($R^2$ = *p*-F-$C_6H_4$; $R^3$ = H) with $Ru(OAc)_2(p\text{-cymene})$ *but without* $Cu(OAc)_2{\cdot}H_2O$ leads only to 30% yield of **3j** (see ESI,† Scheme S3). These results indicate that the key catalytic species arises from



Scheme 4 Proposed mechanism.

the Ru(II) catalysed dehydrogenation of **1a** or from iPrOH with a Ru(OAc)$_2$(*p*-cymene) catalyst. It may then involve the formation of a Ru–H derivative, possibly Ru(H)(OAc)(*p*-cymene), from the reaction of Ru(OAc)$_2$(*p*-cymene) and i-PrOH.[13]



| Conditions | GC-Yield |
|---|---|
| RuCl$_2$(p-cymene)]$_2$ (5 mol%), Cu(OAc)$_2$.H$_2$O (80 mol%), iPrOH ( 2 equiv.), DCE (2 mL), 120 °C | 10% |
| [Ru(OAc)$_2$(p-cymene)] (10 mol%), iPrOH ( 2 mL), 80 °C | 37% |
| [Ru(OAc)$_2$(p-cymene)] (10 mol%), iPrOH ( 2 mL), 100 °C | 56% |

(2)

A possible mechanism for the reaction can be proposed (Scheme 4) based on the initial formation of Ru(OAc)$_2$(*p*-cymene).[14–16] The alcohol **1a** is expected to be dehydrogenated into the ketone **5**, upon coordination to the Ru(II) centre, as PhCOCH$_2$Ph with no coordinating group does not lead to the α-alkylated product **3**. This reaction is expected to release AcOH and a Ru–H(OAc)Ln species.[7,13] This latter species with the additional action of the Cu(II) Lewis acid[17] should favour the formation of the enolate of the ketone **5** and its addition to the alkene. The ketone **5** is also activated by the species generated from Ru(OAc)$_2$(*p*-cymene) and isopropanol, likely the Ru(H)(OAc)(arene) intermediate,[13] which can deprotonate the ketone more easily than Ru(OAc)$_2$(*p*-cymene)[16] and thus would favour the Michael type reaction leading to product **3**. These processes involve the formal generation of hydrogen that can be trapped by the excess of alkene.

In summary, we have described a mild procedure to perform β sp$^3$C–H bond functionalisation of (2-pyridyl)ethanol derivatives by reaction with activated alkenes in the presence of a [RuCl$_2$(arene)]$_2$ catalyst and of Cu(OAc)$_2$·H$_2$O, without additional base. This reaction proceeds by a tandem dehydrogenation of coordinating alcohol and the alkylation with electrophilic alkenes of the resulting ketone. Interestingly, when acrolein was used as the activated alkene, double alkylation took place and led to original 3-formylcyclohex-3-en-1-yl ketone derivatives. This tandem reaction which can be profitably promoted by Ru(OAc)$_2$(arene) in iPrOH offers potential for further mechanistic investigations, creation of new catalysts and applications that are currently underway.

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