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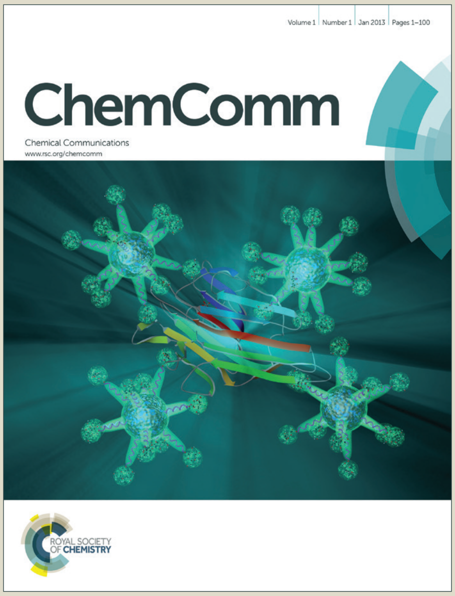

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sp^3C-H bond alkylation of ketones with alkenes via ruthenium(II) catalysed dehydrogenation of alcohols

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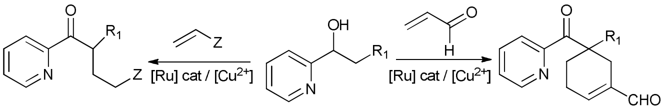
The sp^3C-H bond functionalisation of 2-pyridyl ethanols by reaction with alkenes, in the presence of $[RuCl_2(arene)]_2$ catalyst and $Cu(OAc)_2.H_2O$, is performed under mild conditions without additional base. This reaction proceeds by a tandem alcohol dehydrogenation/alkylation with alkenes of the resulting ketone at its α sp^3C-H bond.

The functionalisation of sp^3C-H bonds attracts interest for 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^3C-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 functionalisation of sp^3C-H bond at β position of alcohols, by alkylation with alkenes, has not been reported yet, in spite of the well-established hydrogen borrowing reactions especially with 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 to investigate the consecutive catalytic alcohol dehydrogenation and neighbouring sp^3C-H or sp^2C-H bond functionalisations. 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]

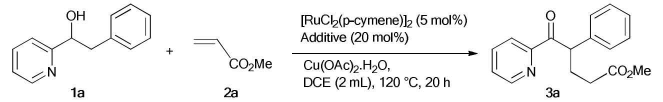
Here we report the Ru(II) catalysed dehydrogenation of 2-pyridyl alcohols in the presence of $Cu(OAc)_2.H_2O$ and the subsequent alkylation at the α position of the resulting ketones with alkenes, and with acrolein, the double alkylation and intramolecular aldol condensation, formally via sp^3C-H bond functionalisation. We also show that the 2-pyridyl ketone can be alkylated with alkene at the α-position of the carbonyl using $Ru(OAc)_2$(p-cymene) catalyst but in the presence of isopropanol (Scheme 1).



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

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 $Cu(OAc)_2.H_2O$ (1 equiv.) which surprisingly led at 120 °C for 20 h to the α-alkylated ketone **3a** (entries 1-2). Interestingly, in the absence of additive, **3a** was produced in 53% yield (entry 3 and Table **S1**). The reaction thus required the presence of both $[RuCl_2$(*p*-cymene)$]_2$ and $Cu(OAc)_2.H_2O$ (entries 4-5). Good results were obtained using only 0.8 equiv. of $Cu(OAc)_2.H_2O$ without air (entries 6-7 and Table **S2**). 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 68% isolated yield (entries 11-12). Using $Ru(OAc)_2$(*p*-cymene) as the catalyst is also moderately operative with $Cu(OAc)_2.H_2O$ (entry 13) (Table **S3**).

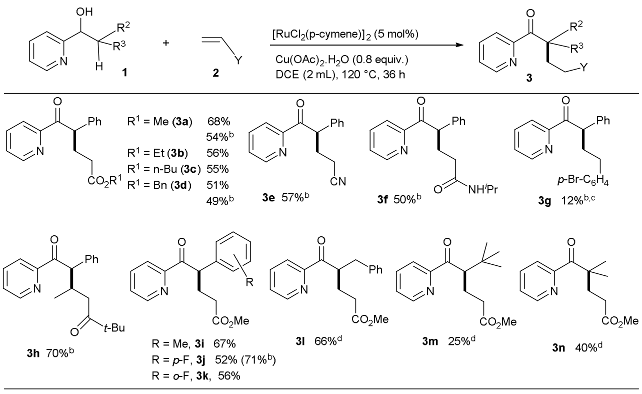
Table 1. Ruthenium(II)-catalysed sp^3 C-H bond alkylation of benzyl 2-pyridyl methanol **1a** with methyl acrylate **2a**[a]



Entry	**2a** (equiv.)	Additive	$Cu(OAc)_2.H_2O$(eq.)	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*-cymene)]$_2$ (5 mol%), additive (20 mol%), $Cu(OAc)_2.H_2O$ (0.8-1 equiv.), DCE (2 mL), 120 °C, 20 h. [b] Detected by GC, in parenthesis, isolated yields of **3a**. [c] Without Ru catalyst. [d] Under air. [e] 7.5 mol% of [RuCl$_2$(*p*-cymene)]$_2$. [f] Run in 0.5 mmol scale, 36 h. [g] In toluene, 150 °C. [h] 10 mol% of [Ru(OAc)$_2$(*p*-cymene)] was used. [i] Less than 5% of ketone 2-PyCOCH$_2$Ph 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.



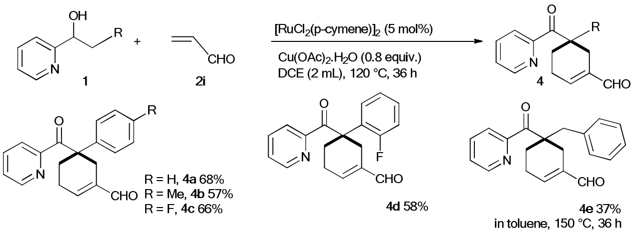
[a] **1** (0.5 mmol), **2** (2 mmol), [RuCl$_2$(p-cymene)]$_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (0.8 equiv.), DCE (2 mL), 120 °C, 36 h. [b] toluene, 150°C, 20 h. [c] Detected by GC. [d] toluene, 150°C, 36 h.

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

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$_3$CH=CHCO*t*-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 has then been 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 give the derivatives **3l-n** in 25-66% yields.

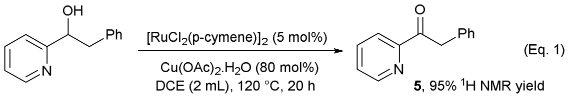
The reaction of **1a** with 4 equiv. of acrolein under similar conditions selectively led to the dicarbonyl cyclic derivative **4a** in 68% isolated yield (Scheme 3). This compound **4a** results from a formal double Michael addition to acrolein of the enolate of ketone **5,** arising from oxidation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



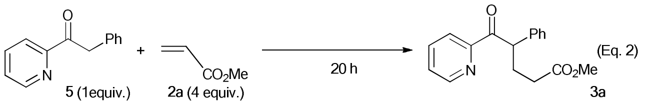
Scheme 3. Ru(II)-catalysed sp^3 C-H alkylation of 2-pyridyl ethanol derivatives with acrolein

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 the derivative **4e** in 37 % yield, resulting from to 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 a formal 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*-cymene)]$_2$ and $Cu(OAc)_2.H_2O$, the alcohol **1a** was transformed into the (2-pyridyl)benzyl ketone **5** (eq. 1). (see also SI Scheme S2)

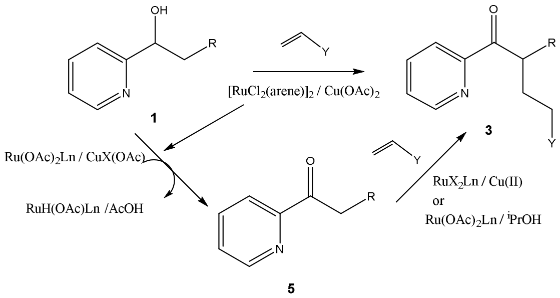


The alkylation of the ketone **5** with methyl acrylate **2a** was then attempted: by action of both [RuCl$_2$(*p*-cymene)]$_2$ (5 mol%) and Cu(OAc)$_2$ (0.8 equiv.), but in the presence of *i*-PrOH (2 equiv), the alkylated ketone **3a** was obtained in only 10% GC-yield (Eq. 2). However when this reaction was performed in the presence of 10 mol% of Ru(OAc)$_2$(*p*-cymene) in *i*-PrOH at 100 °C *without addition of Cu(OAc)$_2$*, **3a** was obtained in 56% GC-yield. Whereas in DCE instead of isopropanol the alcohol **1f** (R^2=*p*-F-C$_6$H$_4$*;* R^3=H) with Ru(OAc)$_2$(*p*-cymene) *but without $Cu(OAc)_2.H_2O$* leads only to 30 % yield of **3j**. (see SI, Scheme S3) These results indicate that the key catalytic species arises from the Ru(II) catalysed dehydrogenation of **1a** or from *i*PrOH with 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%), $Cu(OAc)_2.H_2O$ (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%

A possible mechanism of 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**, on coordination to the Ru(II) centre, as PhCOCH$_2$Ph with no coordinating group did 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.



Scheme 4. Proposed mechanism

Conclusions

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 [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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