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Ruthenium(II)-catalyzed switchable C3-alkylation *versus* alkenylation with acrylates of 2-pyridylbenzofurans *via* C–H bond activation‡

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We documented an interesting observation of the ruthenium(II)-catalyzed benzofuran C-H activation and subsequent functionalization with acrylates that reveals that a simple base can switch the process from alkylation to alkenylation.

The transition metal catalyzed carbon–carbon and carbon–hetero atom bond formations *via* the activation of sp^2 and sp^3 C–H bonds is recognized as a powerful alternative to the classical cross-coupling reactions involving a preformed organometallic partner.[1] Since the discovery of the Ru(0)-catalyzed chelation-assisted C–H bond functionalization and subsequent alkylation *via* insertion of olefin into the (C–Ru–H) Ru–H bond and reductive elimination by Murai and co-workers in 1993,[2] this reaction has been extensively investigated by employing various transition metal complexes.[3] However, the olefins with conjugation were found not to perform this alkylation, such as α,β-unsaturated acceptors.[4] Interestingly, rare reports on the utilization of conjugated olefins such as acrylates in these directed C–H alkylation reactions have appeared only recently with ruthenium (II)-complexes,[5] favoured by strongly chelating directing groups,[5b] whereas there are several examples since 2011 on alkenylation with acrylates employing the Ru(II)/Cu(II) catalytic system.[6] Thus, it is a challenging task to design efficient catalytic systems for tuning the alkylation over alkenylation and *vice versa*.

Benzofuran is one of the commonly encountered structural units in the natural products and pharmaceutically important compounds.[7] The functionalization of benzofurans *via* C–H activation is attractive because this enables an efficient approach for various analogues from simple precursors.[8] The 2-(2-pyridyl)benzofuran derivatives have recently been identified as promising scaffolds in the PET imaging of β-amyloid (Aβ) plaques and thus for diagnosis and the discovery of effective therapeutic agents for Alzheimers.[9] However, as the reports on either the synthesis or the functionalization of 2-(2-pyridyl)benzofurans are scarce, the C–H activation and selective functionalization of 2-(2-pyridyl)benzofurans will provide simple tactics and promote further advances with this class of compounds.[10] Recently, we showed that an acyl directing group in 2-aroylbenzofuran could allow the insertion of an acrylate into the C3–H bond of furan, but more importantly that the nature of the catalyst could selectively lead to the branched insertion product ($RuCl_2(PPh_3)_3$) or to the linear insertion product {$[RuCl_2(p\text{-cymene})]_2$}.[5a] Of course the, alkylation took place due to the preference of the RCO directing group. Thus it was of interest to understand how different directing groups could selectively orchestrate the insertion leading to alkylation or favour β-elimination and thus alkenylation.[11]We now wish to report our initial findings and to show for the first time how acrylates can, *via* ruthenium(II) C–H bond activation, simply lead to alkylation or alkenylation of heterocycle C–H bonds [Figure 1 (a) and (b) respectively]. We reasoned that due to the strong donation of the pyridine directing group, the Ru–C bond in the intermediate ruthenacycle is expected to be more polarized and thus favour the coordination and insertion of the olefin based upon the electronic preferences i.e the electrophilic β-carbon of the acrylate binding to nucleophilic carbon providing the linear alkylation product. This was indeed observed, but in addition the conditions for selective alkylation or alkenylation were discovered.

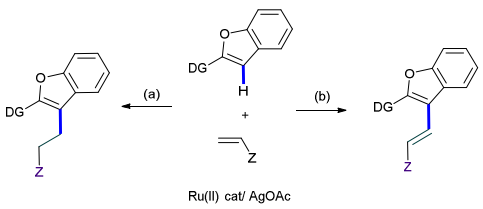
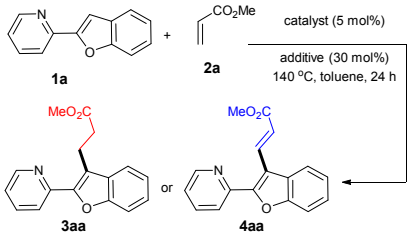


Figure 1. Proposal for the selective alkylation or alkenylation with acrylates

Table 1: Optimization of reaction conditions for directed C–H functionalization[a] [b]



S.No	Catalyst	Base	Additive	**3aa**	**4aa**[b]
1	$Ru(PPh_3)_3Cl_2$	K_2CO_3	AgOAc	no	77
2	$Ru(PPh_3)_3Cl_2$	absence	AgOAc	75	no
3	$Ru(PPh_3)_3Cl_2$	Na_2CO_3	AgOAc	no	74[c]
4	$Ru(PPh_3)_3Cl_2$	Cs_2CO_3	AgOAc	no	66[d]
5	$Ru(PPh_3)_3Cl_2$	$NaHCO_3$	AgOAc	no	63[e]
6	$Ru(PPh_3)_3Cl_2$	NaOAc	AgOAc	no	42[f]
7	$Ru(PPh_3)_3Cl_2$	K_2CO_3	$Cu(OAc)_2$	no	67
8	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	AgOAc	no	69
9	$[Ru(p\text{-cymene})Cl_2]_2$	absence	AgOAc	66	no
10	$Ru(PPh_3)_3Cl_2$	absence	$Cu(OAc)_2$	31	43

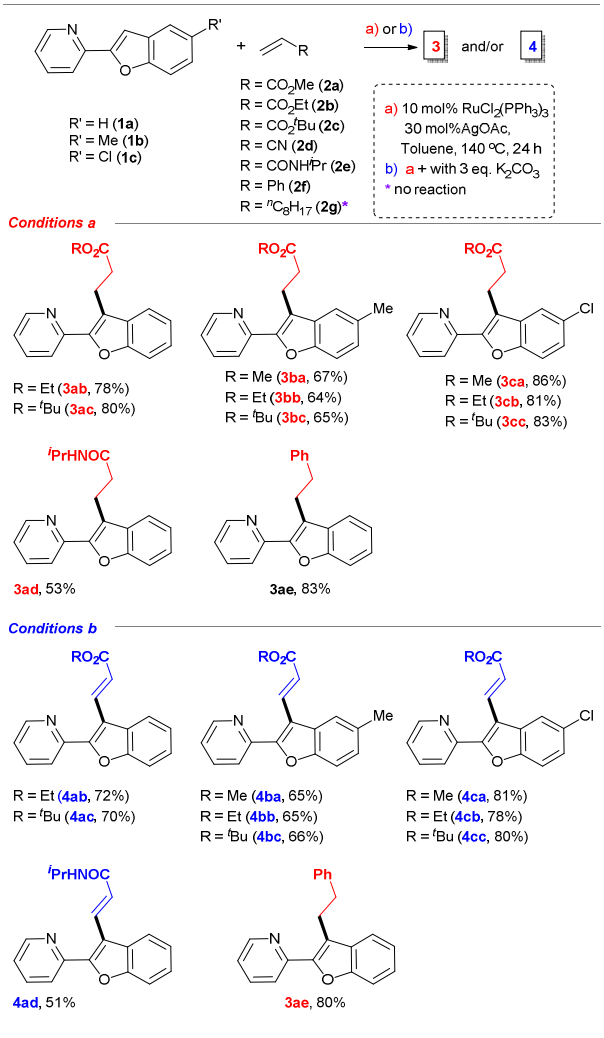
[a] *reagents & conditions*: benzofuran (1 eq.), methyl acrylate (3 eq.), catalyst (5 mol%), K_2CO_3 (3 eq. unless otherwise mentioned), additive (30 mol%), 140 °C, toluene, 24 h. [b]isolated yield after column chromatographic purification, [c]25% of **1a** was recovered, [d]63% of **1a** was recovered, [e]61% of **1a** was recovered, [f]41% of **1a** was recovered.

Our investigations in this regard started with the reaction of 2-pyridyl benzofuran and methyl acrylate in the presence of $RuCl_2(PPh_3)_3$, AgOAc and in the presence of K_2CO_3 in toluene at 140 °C for 24 h. Surprisingly the alkenylated product **4aa** formation with complete linear selectivity has been observed. The linear selectivity was anticipated, however, the observed complete cross-dehydrogenative coupling without any alkylation product was surprising, since no oxidant was employed such as Cu(II) salt.[5a] However, considering the fact that the base was employed in excess and that in Heck-like couplings it is known that the base facilitate the final reductive elimination step, the same reaction was attempted in the absence of base.[12] Interestingly, when the reaction was conducted under identical conditions except in the absence of base, the linear alkylation product **3aa** was obtained exclusively. This important observation revealed that with this Ru (II)-complex, the alkylation reactions are proceeding through the ruthenacycle formation followed by the commonly proposed coordinative insertion mechanism and that the involvement of a Ru–H intermediate is not necessary.

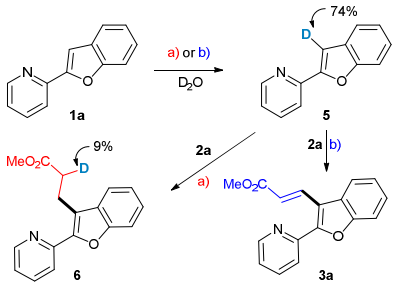
Next, the compatibility of other bases has been studied. As summarized in Table 1, with many of the other bases employed the reactions are incomplete and the starting **1aa** was recovered in substantial amounts. When, $Cu(OAc)_2$ was used as an additive in place of AgOAc, the reaction in presence of base provided **4aa** in comparable yields. However, when there was no base, unlike with AgOAc, where the alkylation reaction was exclusive, with $Cu(OAc)_2$, the products resulting from both the alkylation and the alkenylation were obtained in a 3:4 ratio. Next the $[Ru(p\text{-cymene})Cl_2]_2$ has been examined as a catalyst for these transformations. The reactions are conducted under similar conditions and the results are comparable. In presence of base, **4aa** was obtained with 69% yield, whereas in the absence of base, with the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst also, the linear alkylation product **3aa** was obtained exclusively. This is quite important, as it reveals that with both the ruthenium-complexes, the course of the reactions seems to be similar.

Having discovered two complementary conditions for alkylation or alkenylation, we next explored the generality of these reactions by employing a wide range of olefins. Table 2 summarizes the results obtained with the alkylation and alkenylation reactions. Various acrylates such as ethyl-, and tert.butyl- (**2b** and **2c**,) gave the corresponding alkylation or alkenylation products in moderate to good isolated yields. However, the reactions with *N*-isopropylacrylamide (**2d**) were found to be sluggish and the products were obtained in poor yields. With styrene (**2e**), the linear alkylated product was obtained exclusively even in the presence of K_2CO_3. As shown in Table 2, the presence of the electron withdrawing substituent on the benzofuran ring has, at most, only nominal influence on the selectivity. Interestingly, when a methyl group is present in place of chlorine, the yields were found to drop slightly. These observations indicate that the C–H bond strength of the C3 carbon of benzofuran and the steric environment around the olefin has some influence on the yield of the reaction.

Table 2: Scope of the Ru(II)-catalyzed alkylation *versus* alkenylation of 2-(2-pyridyl)benzofuranswith acrylates.



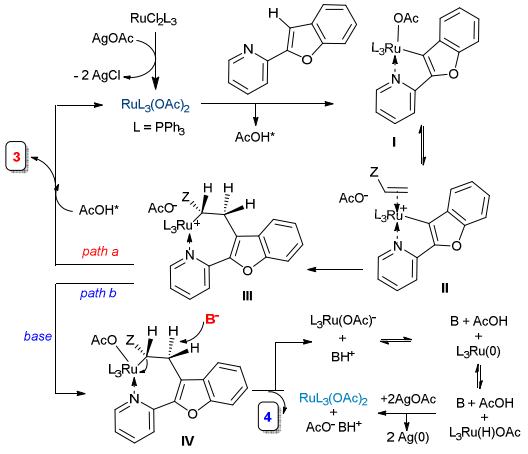
Deuterium labelling experiments have been carried out in order to understand the course of the deprotonation and also the possibility of the hydrometalation or carbometalation followed by proto demetalation. The reactions were conducted in the presence of D_2O and under the conditions A and B, excluding the olefin. The deuterium incorporation was observed at the C3 position of benzofuran. The C3-deuterated benzofuran **5** reacted with acrylate under the optimized conditions. As shown in Scheme 1, only a nominal incorporation of deuterium at the α-position of the alkylated product was observed.



Scheme 1. Deuterium labelling experiments.

Although the mechanism cannot be demonstrated yet, we extend the following proposal to explain these two reactions. The reaction of the $RuCl_2(PPh_3)_3$ complex with 2 eq. of AgOAc generates $Ru(OAc)_2(PPh_3)_3$.[13,14] The coordination of the pyridyl nitrogen and the subsequent acetate-mediated deprotonation leads to the intermediate ruthenacycle **I** and releases AcOH. The easy dissociation of the AcO–Ru(II) bond from complex **I**, especially in the presence of AcOH, favours the coordination of the olefin to the cationic intermediate **II**. Due to the polar Ru–C bond present in complex **II**, the olefin insertion takes place with addition of the nucleophilic Ru-C carbon atom to the acrylate electrophilic β-carbon to give the linear insertion product precursor **III**. When there is no base present, this intermediate, upon protodemetallation by the released AcOH, affords the linear alkylation product **3** and thus regenerates the ruthenium acetate complex. When the base is present, since the β- elimination (commonly encountered in Heck-coupling) is not possible (as it requires that M–C_α and C_β–H bonds to align in a *syn*-coplanar arrangement), we propose that the base abstracts the β-proton at the anti-position of the Ru atom to form the alkenylation product **4**.[15]

Scheme 2. Proposed mechanism for the alkylation *vs.* alkenylation



Conclusions

In conclusion, our current investigations reveal two important observations in the directed C–H activation and functionalization. First, the donating ability of the chelating group *inter alia* the electronic factors override the steric influence when the Ru–C bond is polar. Secondly, we show for the first time that the presence of base avoids alkylation and favours, in the absence of oxidant (Cu^{II}), dehydrogenative cross coupling processes *via* C–H activation. We believe that these findings will provide fresh impetus for further efforts on understanding how the nature of the substrate, catalyst and base will be fine-tuned in order to achieve the alkylation or akenylation with the desired regioselectivity.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Characterization data and spectra of all new compounds]. See DOI: 10.1039/b000000x/

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15 The exclusive alkylation that resulted in the case of styrene (even in the presence of base), indicates the possible synergetic assistance of the carboxylate group either in stabilizing the alkylruthenium intermediate resulting from the coordinative insertion or the deprotonation of the *syn*-hydrogen.

Ruthenium(II)-catalyzed switchable C3-alkylation *verses* alkenylation with acrylates of 2-pyridylbenzofurans *via* C–H bond activation

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