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Mild *N*-Alkylation of Amines with Alcohols Catalyzed by the Acetate $Ru(OAc)_2(CO)(D\textit{i}PPF)$ Complex

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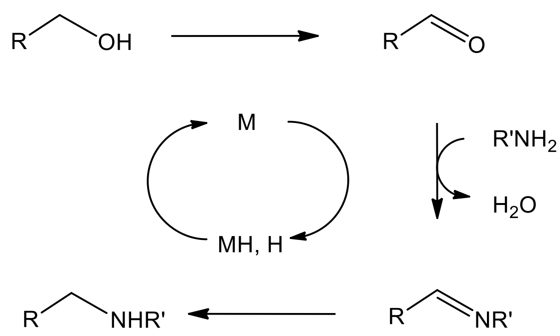
Abstract: The acetate complex $Ru(OAc)_2$(D*i*PPF) (**2**) obtained from $Ru(OAc)_2(PPh_3)_2$ (**1**) and 1,1'-bis(diisopropylphosphino)ferrocene (D*i*PPF) reacts cleanly with formaldehyde affording $Ru(OAc)_2$(CO)(D*i*PPF) (**3**) in high yield. The monocarbonyl complex **3** (0.4-2 mol %) efficiently catalyzes the *N*-alkylation of primary and secondary alkyl and aromatic amines using primary alcohols ROH (R = Et, *n*Pr, *n*Bu, $PhCH_2$) under mild reaction conditions (30 - 100 °C) with an alcohol / amine molar ratio of 10-100. Formation of the monohydride RuH(OAc)(CO)(D*i*PPF) (**4**) has been observed by reaction of **3** with *i*PrOH in the presence of NEt_3 at RT through an equilibrium reaction.

Keywords: *N*-alkylation • amines • alcohols • borrowing hydrogen • ruthenium

The selective formation of C-N bonds is a reaction of high relevance for the synthesis of amine and heterocycle compounds for fine and pharma chemicals.[1] As a matter of fact, the preparation of several drug molecules involves *N*-substitution transformations, which are usually performed by reaction of amines with alkylating agents or via reductive amination. In this context, the catalytic *N*-alkylation of amines using environmentally friendly alcohols as alkylating reagents and affording water as only byproduct, is an attractive atom-economic way for the C-N bond formation, widely studied in academia and of great interest for industrial applications.[2] It is generally accepted that this reaction may occur through a catalytic borrowing hydrogen approach, in which primary alcohols are dehydrogenated to carbonyl compounds which react with amines, affording imines that are hydrogenated to *N*-alkylated amines (Scheme 1).

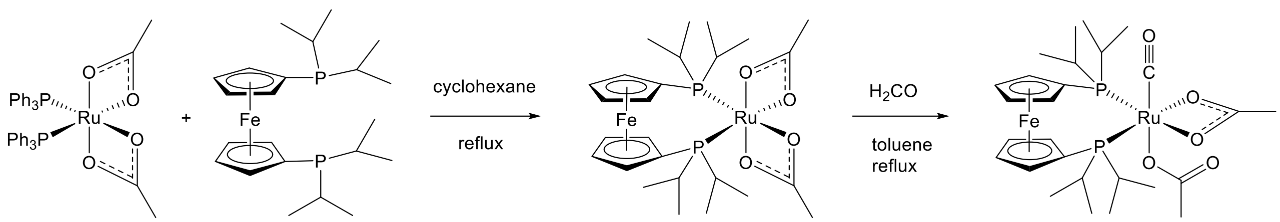


Scheme 1. *N*-alkylation of amines with alcohols via borrowing hydrogen

Main group metal hydroxides and alkoxides were found to catalyze the *N*-alkylation of amines with alcohols under harsh conditions, resulting in low yield and selectivity.[3] In the last decades, Ir, Ru[2] and more recently Mn and Fe[4] and have attracted a great deal of attention for *N*-alkylation via borrowing hydrogen. Examples of ruthenium catalysts generated *in situ* entails the use of the precursors $RuCl_3{\cdot}nH_2O$,[5] $Ru_3(CO)_{12}$,[6] $[RuCl_2(p\text{-cymene})]_2$[7] $[Ru(COD)Cl_2]_n$[8] $RuHCl(CO)(PPh_3)_3$,[9] and $RuH_2(CO)(PPh_3)_3$[10] in combination with phosphanes, phosphates and nitrogen ligands. Conversely, well-defined catalysts are $RuCl_2(PPh_3)_3$,[11] $RuH_2(PPh_3)_4$,[12] $RuCl(\eta^5\text{-}C_5H_5)(PPh_3)_2$,[13] [RuCl(*p*-cymene)(PN)]X,[14] RuHCl(CO)(PNY) (Y = N, P),[15] RuCl(CNN)(dppb)[16] and Ru pincer NNN complexes.[17] *N*-alkylation is generally performed at high temperature (typically 120 or 180 °C), primary alcohols are generally more reactive than secondary and long reaction times are required. Therefore, the development of selective catalysts which can work at low temperature is of crucial importance for the application of this relevant sustainable transformation. Monocarbonyl Ru complexes, namely the Dobson catalyst $Ru(OCOCF_3)_2(CO)(PPh_3)_2$[18] and $[Ru(\mu\text{-}OCOC_2F_4OCO)(CO)(PP)]_2$[19] (PP = diphosphane), are active catalysts for alcohol dehydrogenation, which is the first step of the catalytic *N*-alkylation. Recently, the in situ generated complex $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ / (*R*)-BINAP has been found active in the asymmetric C-C coupling between olefin and primary alcohols. [20] It is worth pointing out that the coordination properties of carboxylate ligands, which display moderate stability with relatively high lability, are particularly attracting for catalytic reactions, but no examples of carboxylate Ru complexes have been reported in the *N*-alkylation reaction.

We describe here the straightforward preparation of the acetate complexes $Ru(OAc)_2(CO)_n$(D*i*PPF) (n = 0, 1), bearing the bulky ferrocene diphosphane D*i*PPF.[21] The monocarbonyl acetate complex has been found highly active in the alkylation of primary and secondary amines with primary alcohols under mild reaction conditions. Evidence has been provided for the formation of the monohydride species RuH(OAc)(CO)(D*i*PPF) in the alcohol / amine media.

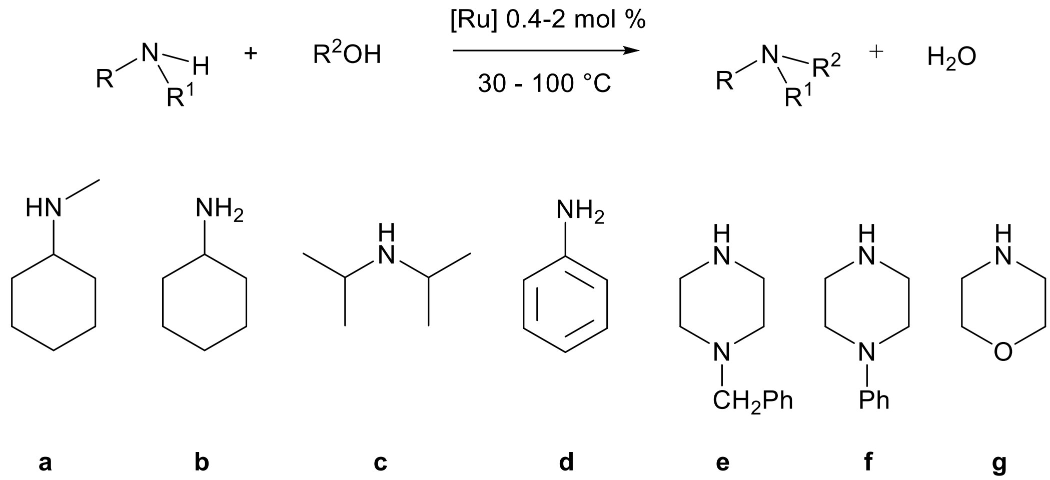
The ruthenium diphosphane compound $Ru(OAc)_2$(D*i*PPF) (**2**) was easily prepared by treatment of the acetate precursor $Ru(OAc)_2(PPh_3)_2$ (**1**) with one equivalent of D*i*PPF in cyclohexane at reflux (4 h, 87 % yield) (Scheme 2).



Scheme 2. Synthesis of $Ru(OAc)_2$(D*i*PPF) (**2**) and $Ru(OAc)_2$(CO)(D*i*PPF) (**3**).

The ^1H and $^{13}C\{^1H\}$ NMR spectra of **2** at RT show two signals for the ferrocene CH moieties, consistent with a rapid displacement of the Ru-O acetate bond *trans* to the P atom. Complex **2** reacts cleanly with formaldehyde (5 equiv) in toluene at reflux within 2 h, affording the monocarbonyl acetate complex **3** in 78 % yield. Alternatively, complex **3** can also be prepared by reaction of **2** with paraformaldehyde in toluene. At RT the $^{31}P\{^1H\}$ NMR spectrum of **3** in CD_2Cl_2 shows a broad singlet at δ = 61.7 ppm ($\Delta\nu_{½}$ = 110 Hz), while the ^1H NMR spectrum exhibits four C-H signals for the ferrocene C_5H_4 moiety and a singlet at δ = 1.92 ppm for the two acetate ligands, indicating an exchange of the OAc^- groups on the NMR time scale at RT. Upon cooling at -75 °C both the ^{31}P and ^1H NMR spectra become more complex, possibly due to the formation of conformers with the bulky isopropyl ferrocene ligand and the different coordination mode of the two acetates (see Supporting Information). The CO stretching of **3** is at relatively low wavelength (1939 cm^{-1}), in agreement with the presence of the electron-reach diphosphane.

The carboxylates complexes **1-3** (0.4-2 mol %) were found active in the *N*-ethylation of *N*-methylcyclohexylamine (**a**) using commercially grade ethanol under mild reaction conditions (Scheme 3). With the diacetate derivative **1**, the tertiary amine NMeEtCy is formed in 25 % at 78 °C (20 h), with a EtOH/NHMeCy = 100 (entry 1, Table 1).



Scheme 3. *N*-alkylation of amines with alcohols catalyzed by ruthenium acetate complexes

Table 1. *N*-ethylatation of methylcyclohexylamine (**a**) with EtOH catalyzed by ruthenium acetate complexes (1 mol %).

Entry	**Complex**	**Ligand or additive (equiv)**	**EtOH/ NHMeCy**	**T [°C]**	**Time [h]**	**Conv[a] [%]**	**Byproducts[a] [%]**
1	**1**		100	78	30	25	3
2	**2**		10	65	15	80	
3	**2**	TFA (15)	10	65	15	96	1
4	$Ru(OAc)_2$(DPPF)		100	78	16	6	< 1
5	$Ru(OAc)_2(CO)(PPh_3)_2$		10	78	29	0	0
6	$Ru(OAc)_2(CO)(PPh_3)_2$	D*i*PPF (1.5)	10	78	25	51	5
7	$Ru(OAc)_2(CO)(PPh_3)_2$	DPPF (1.5)	10	78	25	1	5
8	**3**		100	78	6	97	< 1
9	**3**		10	65	24	92	1
10	**3**	TFA (10)	10	65	6	98	< 1
11	**3**[b]		10	30	40	68	1
12	**3**[b]	TFA (10)	10	30	40	97	< 1
13	no catalyst		10	78	22	0	-

[a] The conversion was determined by GC analysis. [b] Catalyst loading 2 mol%.

By employment of **2** bearing D*i*PPF 80 % conversion was achieved in 15 h at 65 °C with a lower EtOH/NHMeCy = 10 (entry 2). Interestingly, an increase of rate is observed by addition of CF_3COOH (TFA) (15 equiv, with respect to Ru) to **2**, affording 96 % of the ethylated amine (entry 3). The use of the corresponding DPPF[2121] complex $Ru(OAc)_2$(DPPF) leads to poor conversion (6 %) (entry 4). The monocarbonyl derivative $Ru(OAc)_2(CO)(PPh_3)_2$ gives no conversion under these catalytic conditions (entry 5). Addition of D*i*PPF (1.5 equiv) to the latter derivative affords 51 % of NMeEtCy at 78 °C in 25 h, whereas with DPPF poor conversion is achieved (1 %), indicating that the more basic D*i*PPF leads to a more active catalytic species, with respect to DPPF (entries 6, 7). Employment of the isolated monocarbonyl D*i*PPF complex **3** results in 97 % conversion in 6 h at 78 °C, whereas at 65 °C 92 % of product is achieved in 24 h, with EtOH/NHMeCy = 100 and 10 respectively (entries 8, 9). The higher catalytic activity of **3** with respect to the in situ generated catalyst $Ru(OAc)_2(CO)(PPh_3)_2$ / D*i*PPF can be ascribed to the incomplete diphosphane substitution. Similar to **2**, addition of TFA (10 equiv) to **3** at 65 °C results in an acceleration effect, affording 98 % of product in 6 h (entry 10). Interestingly, by performing the reaction at 30 °C with **3** (2 mol %), 67 % of NMeEtCy is attained in 40 h (entry 11), whereas addition of TFA, resulted in 97 % of product (entry 12), indicating that quantitative *N*-alkylation can be achieved *at low temperature*. Control experiments carried out with 1.5-50 equiv of TFA with respect to **3**, show that the faster conversion of **a** into NMeEtCy has been observed with 3-10 equiv of acid (TOF up to 200 h^{-1} at 50 % conv. at 65 °C, see Figure S-31 of SI), suggesting that the *N*-alkylation occurs in a suitable pH window. An increase of rate by addition of acids has previously been reported for the $RuH_2(CO)(PPh_3)_3$ / xantophos system,[1010] and for $Ru(OCOCF_3)_2(CO)(PPh_3)_2$[18] in the alcohol dehydrogenation. By carrying out the reaction without Ru catalysts no *N*-ethylation is observed after 22 h (entry 13). In addition, no formation of ethyl acetate was observed during the *N*-ethylation of **a** with **3**, suggesting that the in situ generated acetaldehyde undergoes a faster attack of the amine with respect to ethanol.

Complex **3** (0.4-1 mol %) shows catalytic activity for the *N*-alkylation of primary and secondary amines with primary alcohols (Scheme 3). Cyclohexylamine (**b**) reacts with EtOH affording quantitatively the tertiary amine NEt_2Cy in 21 h at 78 °C (entry 1, Table 2), via the NHEtCy intermediate detected by GC analysis.

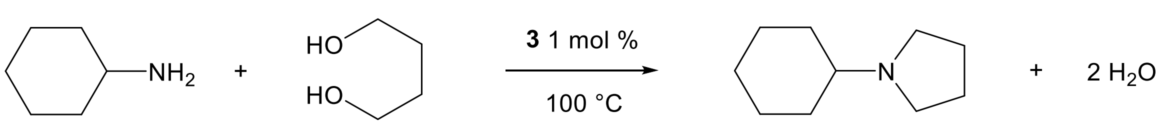
Table 2. *N*-alkylation of amines with alcohols catalyzed by **3** (1 mol %).

Entry	**Amine**	**Alcohol**	**Alcohol/ Amine**	**T [°C]**	**Time [h]**	**Conv.[a] [%]**	**Byproducts[a] [%]**
1	**b**	EtOH	100	78	21	96[b]	3
2	**c**	EtOH	100	78	24	15	1
3	**d**	EtOH	10	65	24	70[b]	2
4	**e**	EtOH	10	65	5	100	-
5	**f**	EtOH	10	65	5	99	1
6	**g**	EtOH	10	65	6.5	100	-
7	**a**	MeOH	10	65	24	10	1

8	**a**	MeOH	10	100	24	16	1
9	**a**	*n*PrOH	10	65	27	68	1
10	**a**	*n*BuOH	10	65	30	60	7
11	**a**	$PhCH_2OH$	5	100	48	87	1
12	**a**	*i*PrOH	10	65	36	0	1
13	**b**	1,4-butanediol	2	100	30	87	10[d]
14	**e**[c]	EtOH	10	78	15	100	-

[a] The conversion was determined by GC analysis and assessed by ^{1}H NMR spectroscopy.
[b] Dialkylated product. [c] Catalyst loading 0.4 mol%. [d] Monoalkylated product.

The bulky amine NH*i*Pr_2 (**c**) leads to NEt*i*Pr_2 in poor conversion (15 %) (entry 2), whereas aniline (**d**) gives NEt_2Ph (70 %) at 65 °C after 24 h (entry 3). Conversely, the drug precursors *N*-benzylpiperazine (**e**), *N*-phenylpiperazine (**f**) and morpholine (**g**) were quantitatively ethylated at 65 °C to the corresponding amines in 5 h (entries 4, 5) and 6.5 h (entry 6), indicating that more basic and less sterically hindered amines undergo faster alkylation with **3**. Experiments carried out with **a** and using different primary alcohols show that while with MeOH poor conversion is attained at 65 and 100 °C (10 and 16 %, entries 7 and 8), *n*PrOH and *n*BuOH afforded the corresponding amines NMeRCy (R = Pr, Bu) in 68 and 60 % yield in 27 and 30 h (entries 9 and 10). With benzyl alcohol $NMe(CH_2Ph)Cy$ is formed in 87 % yield at 100 °C after 48 h (entry 11), whereas the use of the secondary alcohol *i*PrOH gave no conversion at 65 °C (entry 12). The use of the 1,4-butanediol in molar ratio 2/1 with respect to the primary amine **b** afforded the cyclic tertiary amine *N*-cyclohexylpyrrolidine in 87 % yield at 100 °C after 30 h, the reaction efficiently occurs at low alcohol / amine ratio (entry 13, Eq 1).

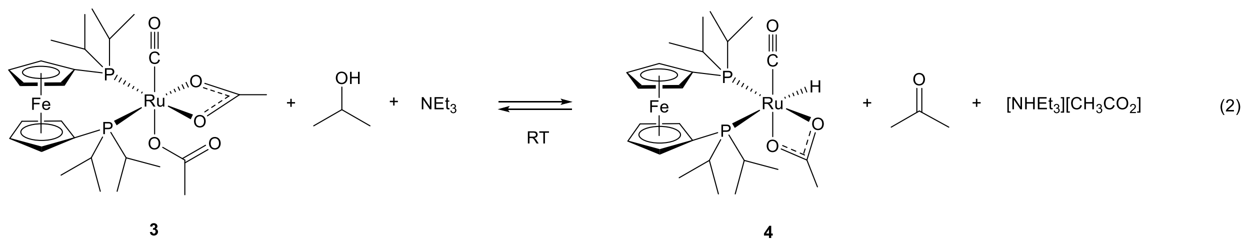


(1)

b

Although the dehydrogenation step is thermodynamically favored for secondary alcohol compared to primary ones,[22] it is likely that the higher reactivity of the primary ones is due to easier formation or hydrogenation of the corresponding aldimines with respect to ketimines. To show the practical potential of catalyst **3**, the amine 1-benzyl-4-ethylpiperazine (1.87 g, 81 %) was obtained from **e** (1.98 g) and ethanol (5.7 mL) using 30 mg of **3** (0.4 mol %) at 78 °C in 15 h (entry 14, see SI).

In the catalytic *N*-akylation reaction the formation of a Ru hydride species is expected during the alcohol dehydrogenation (Scheme 1).[23] Complex **3** is soluble in alcohols (EtOH, *i*PrOH) affording a broad ^{31}P NMR singlet rather similar to that observed for **3** in CD_2Cl_2. Interestingly, addition to **3** of the weakly coordinating NEt_3 amine (20 equiv) at RT in 2-propanol leads quickly to the monohydride RuH(OAc)(CO)(D*i*PPF) (**4**), which equilibrates with the dicarboxylate **3** (**4** / **3** = 1 / 9 molar ratio) (Eq 2).



The ^{31}P{^{1}H} NMR spectrum of **4** shows two doublets at δ = 80.0 and 24.6 ppm (external $CDCl_3$ lock) with a small ^{2}J(P,P) of about 7.7 Hz, the high field resonance being attributed to the P *trans* to the H, displaying a ^{2}J(H,P) of 135 Hz (see SI). Complex **4** also forms by reacting **3** with dihydrogen (4 atm) in [D_8]toluene through an equilibrium reaction, affording in the ^{1}H NMR spectrum a doublet of doublets at δ = -5.98 ppm for the Ru-H with ^{2}J(H,P) of 31.3 and 133 Hz for the *cis* and *trans* P atoms, respectively, likewise the RuH(CNN)(dppb) system.[24] It is worth pointing out that, while the dinuclear hydride complex [Ru(μ-H)(CO)(BINAP)]$_2$($O_2CC_2F_4CO_2$) has been described as resting state in the alcohol dehydrogenation,[19] the mononuclear species RuHX(CO)(PP) (X = Cl, carboxylate) have been postulated to play a key role in the catalytic cycles of alcohol dehydrogenation[1919] and C-C coupling reactions.[25]

As regards the mechanism of the *N*-alkylation by **3**, it is likely that the monohydride **4** is formed by substitution of one acetate with the alkoxide, generated in the alcohol / amine media, followed by β-H-elimination. The resulting aldehyde reacts with the amine, affording the imine (and water) which gives insertion into the Ru-H bond. Protonation with alcohol leads to the alkylated amine and formation of the Ru-alkoxide which closes the cycle.

In summary, we have shown that the easily accessible carboxylate Ru(OAc)$_2$(CO)(D*i*PPF) (**3**), containing the bulky D*i*PPF diphosphane, displays high activity in the *N*-alkylation of amines with primary alcohols under mild reaction conditions. This system is one of the most active catalysts reported to date, allowing unprecedented mild *N*-alkylation at temperature as low as 30 °C and without the use of additional base or solvents. A monohydride species forms promptly at RT in alcohol in the presence of NEt_3 via an equilibrium reaction. Studies are ongoing to rationalize the acceleration effect of CF_3COOH

and give new insights on the mechanism of the *N*-alkylation reaction, as well as to extend this protocol for other C-X coupling reactions, including the use of chiral diphosphanes in asymmetric catalysis.

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